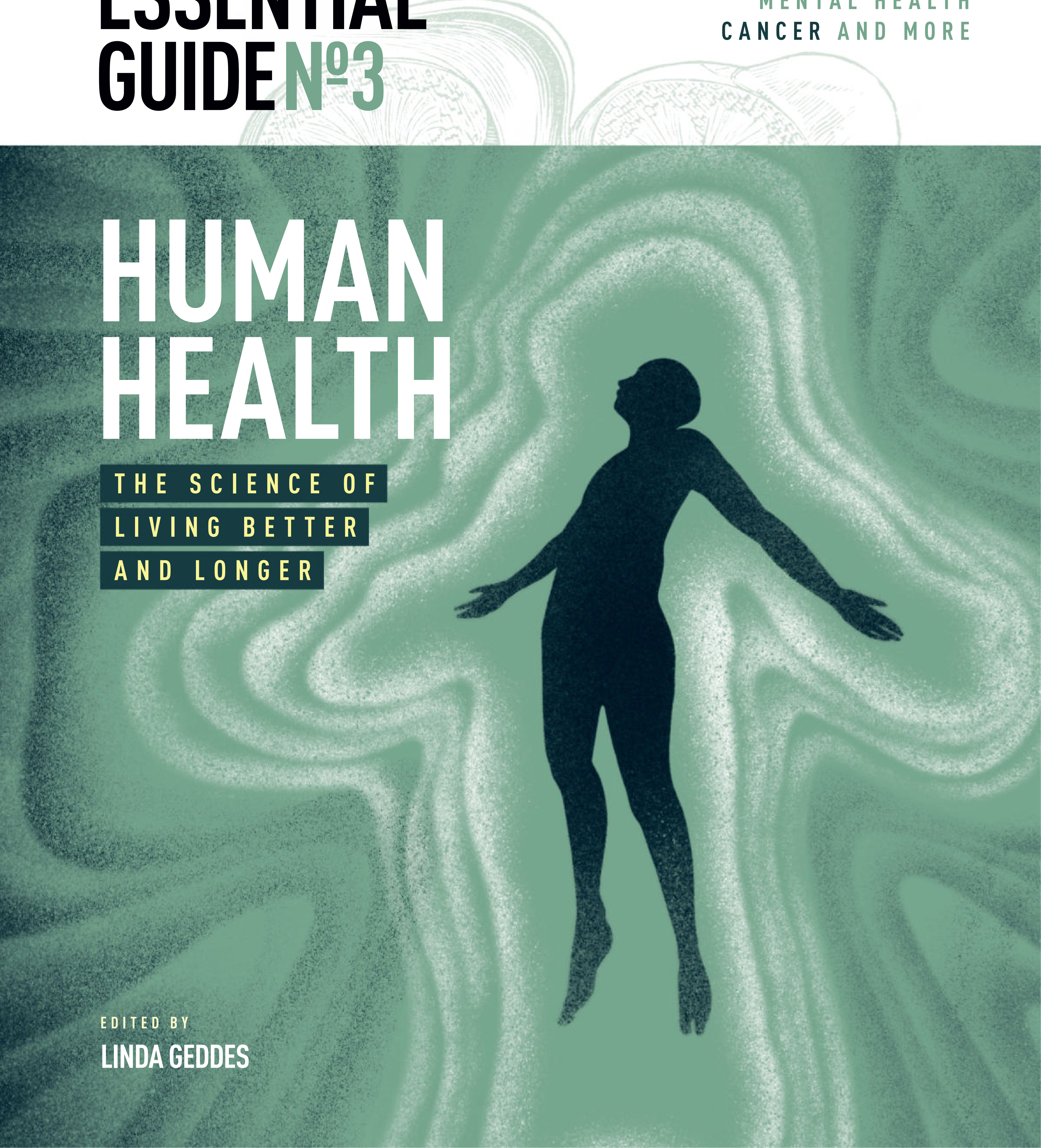
New Scientist

ESSENTIAL GUIDE Nº3

IMMUNITY AND
INFECTIOUS DISEASE
EVERYDAY MALADIES
PHYSICAL HEALTH AND AGEING
MENTAL HEALTH
CANCER AND MORE



HUMAN HEALTH

THE SCIENCE OF LIVING BETTER AND LONGER

EDITED BY
LINDA GEDDES

NEW SCIENTIST ESSENTIAL GUIDE
HUMAN HEALTH

THE coronavirus pandemic has reminded us how much we tend to take our health, both physical and mental, for granted. Yet good health isn't simply the absence of disease. It is a state in which we can adapt to, and cope with, whatever life throws at us – even if we have a chronic disease or disability.

This *Essential Guide* is a newly re-edited and updated collection of material originally published in *New Scientist* magazine, addressing some of the latest thinking on what underlies good physical and mental health: the origins of many common diseases; strategies for tackling them; and how to minimise our chances of falling ill in the first place.

Human health is a huge topic, and what is contained in this *Essential Guide* cannot be exhaustive. Nor is it intended to be medical advice: if you think you are affected by any of the conditions discussed, please seek the advice of a medical professional.

But if you are looking for an overview of the cutting edge of scientific thinking about human health, you're in the right place. I hope you enjoy reading. Feedback is welcome at essentialguides@newscientist.com.

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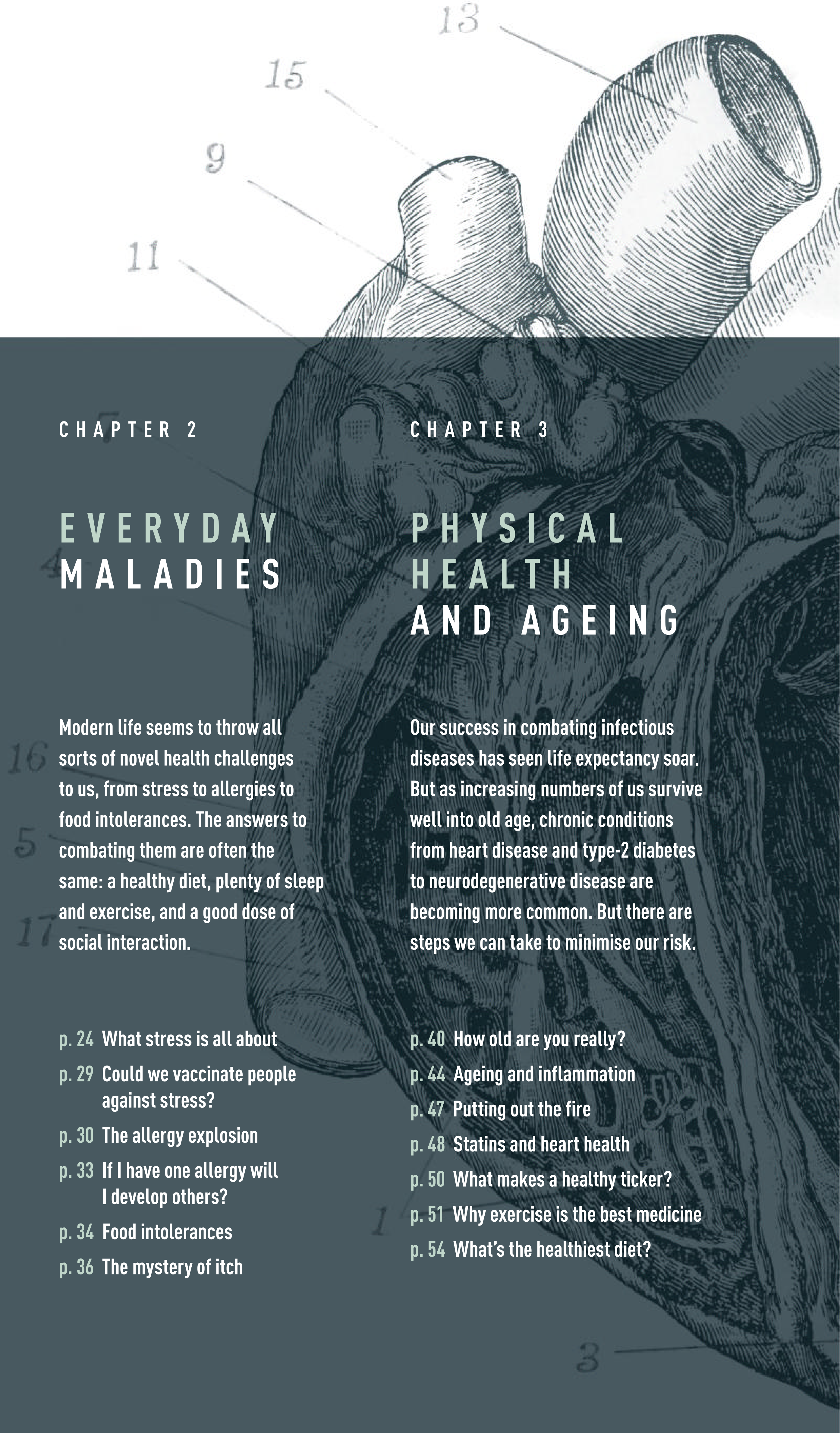

CHAPTER 1

IMMUNITY AND INFECTIOUS DISEASE

More powerful than any drug, the immune system holds the key to human health. When it's working well, we barely notice it, but if it goes awry sometimes fatal infectious and autoimmune diseases result. So how does it work, and what makes it turn against us?

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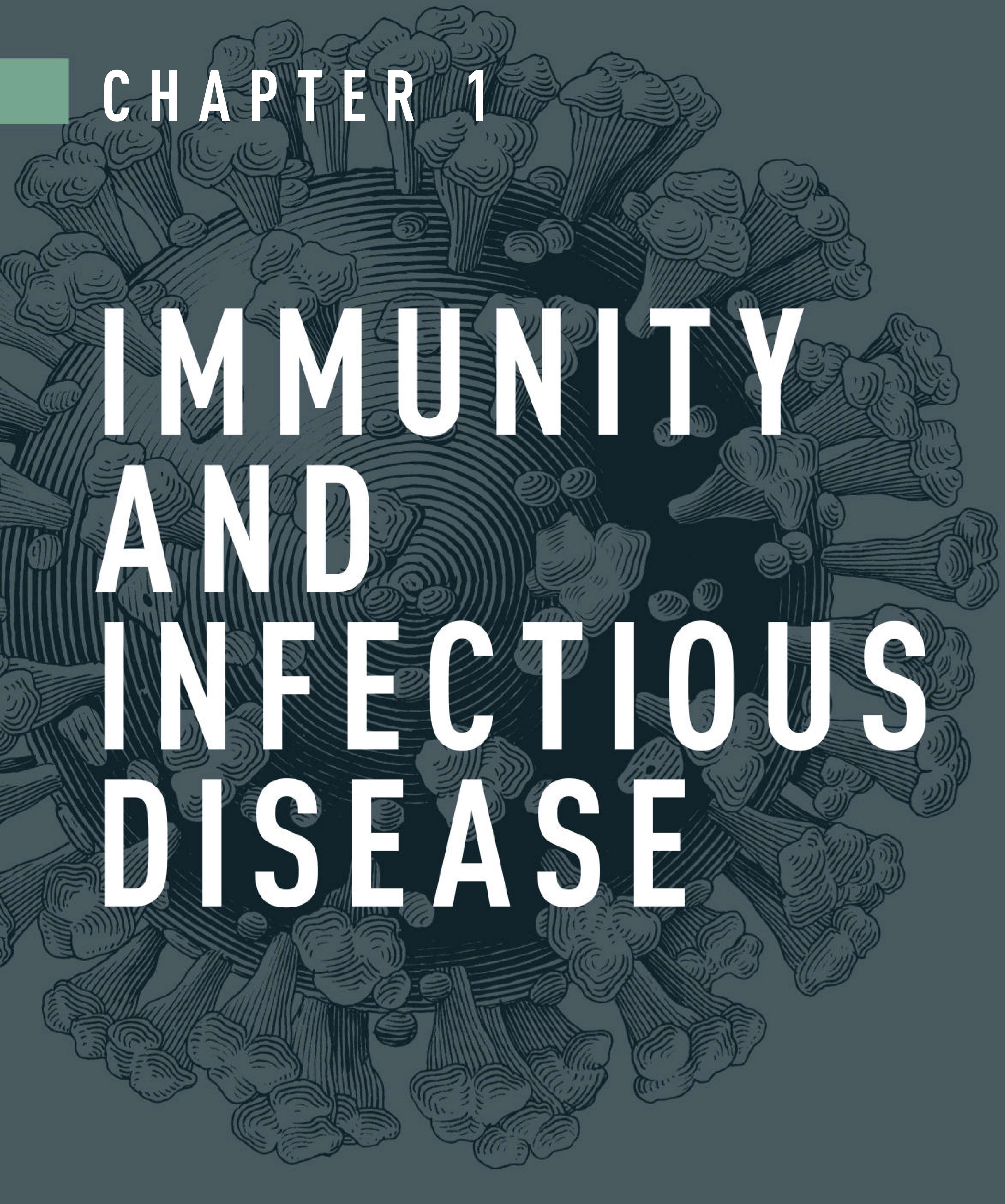


CHAPTER 1

IMMUNITY AND INFECTIOUS DISEASE

Even if we didn't know it before, the coronavirus pandemic has made it plain: the immune system holds the key to human health. More powerful than any drug, every minute of every day it is hard at work defending us from invasion by foreign organism – not just viruses, but bacteria, fungi, and parasites.

When the immune system is working well, we barely notice it, but when it fails, sometimes fatal infectious and autoimmune diseases result. So how does this powerful defence system work, and why does it sometimes turn against us?

HOW THE IMMUNE SYSTEM WORKS

Some people seem to catch everything that is doing the rounds, from coughs and colds to stomach bugs. Other people never seem to get ill. What's their secret? The immune system is vastly complex, and immunology is a relatively young discipline, but over the past two decades we have made significant inroads into understanding this vast and intricate inner world that keeps us safe.

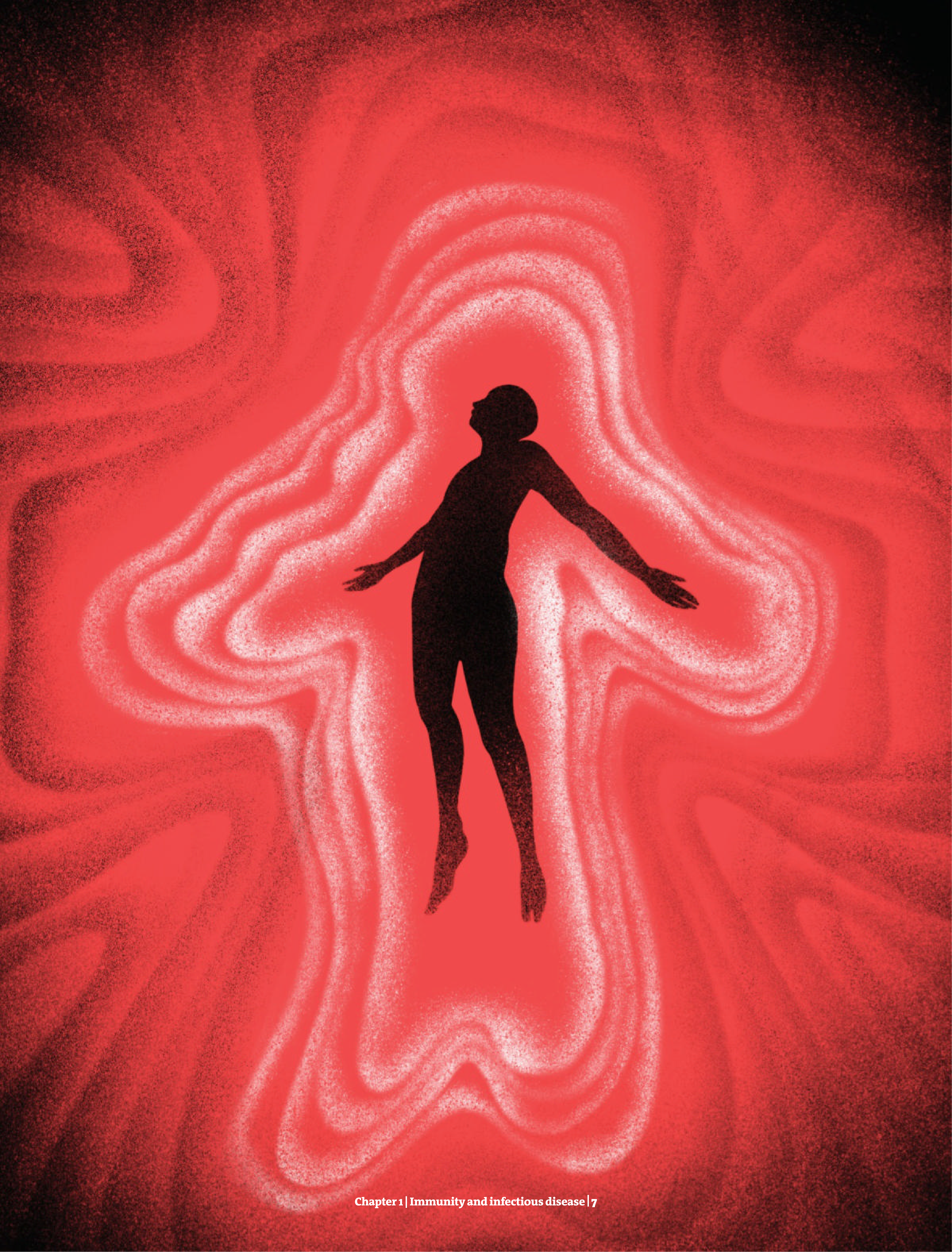
WASH your hands religiously for 20 seconds, avoid touching your face, ensure all poultry is thoroughly cooked, practice safe sex, and, as a last resort, shut yourself away with only your emergency rations for company. The coronavirus pandemic has reminded us of the importance of some of these sensible procedures for avoiding the effects of an infectious agent. But the most important thing standing between you and a possibly deadly disease, whether covid-19, winter flu, salmonella poisoning or HIV/AIDS, is your immune system.

The body has two key lines of defence against foreign invaders: the innate and adaptive immune systems. Innate immunity is the first line of defence, staffed by general-purpose, pathogen-killing cells such as neutrophils and macrophages. The job of these early responders is to try and hold off any potential invaders in the first few days.

If they get past these barriers, the adaptive – or acquired – immune system takes over. The adaptive side is slower and more targeted, reacting to specific pathogens with precision weapons such as T-cells, B-cells and antibodies.

DANIEL STOLLE

The adaptive arm also provides immune memory, which helps prevent you from getting the same disease twice. Cells called memory B-cells recognise ›



pathogens they've previously encountered and trigger a swift and ruthless response if they invade again. This mechanism is at the heart of vaccination. One of the most significant medical developments in history, vaccination is thought to have saved 10 million lives between 2010 and 2015 alone. However, some viruses – notably flu – can mutate to evade immune memory.

And unfortunately, our immune system can go haywire. Sometimes it mistakes elements of our bodies for foreign invaders, launching attack on our own tissues. This leads to the development of autoimmune diseases, such as rheumatoid arthritis or lupus. Other times, it may generate an excessive response to harmless foreign substances, such as pollen, resulting in allergies.

→ Turn to page 30 for more on allergies

An infection occurs when an invading organism breaks through our defences and begins to multiply, triggering tissue damage and disease. Viruses can make us sick by destroying cells or disrupting their normal activities. Bacteria also do this, but they also have a life of their own. They can multiply and crowd out our own tissue, stopping it from working properly, or make toxins which destroy or paralyse our cells.

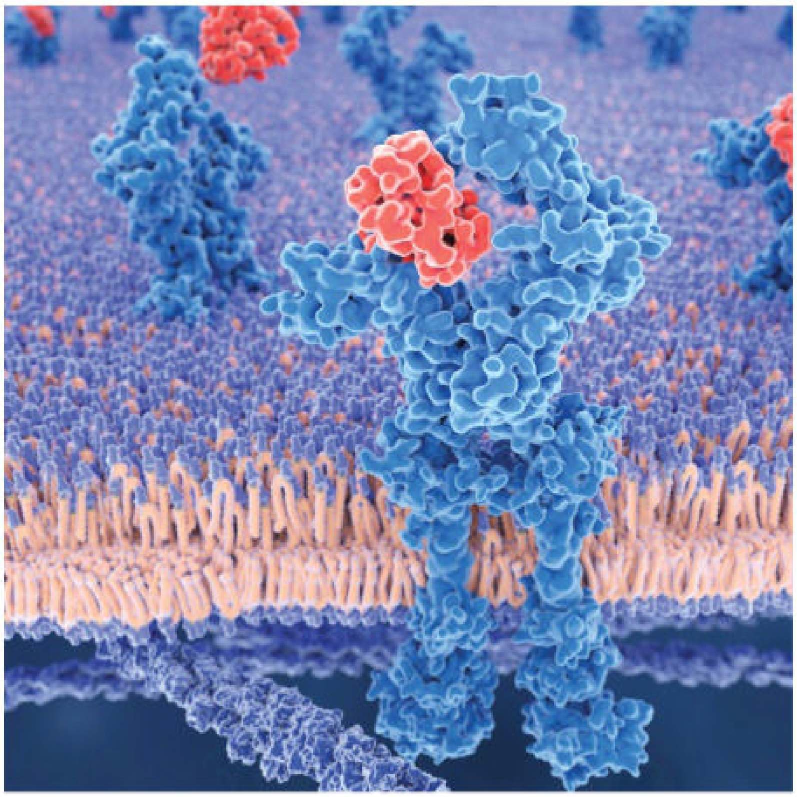
But many of the symptoms we associate with infectious disease are in fact the result of our immune system's reaction to invasion, rather than the bugs themselves. When our body's defences are breached, damaged cells and immune cells called macrophages secrete chemicals known as cytokines. With a name derived from the Greek words for cell (*cyto*) and movement (*kinos*), cytokines coordinate the body's response against infection and trigger inflammation.

One consequence of this is fever. When cytokines hit a brain area called the hypothalamus, it releases hormones that cause various heat-boosting responses. Blood vessels in our skin constrict so less heat is lost at the body's surface. Fat cells start burning energy and our muscles rapidly contract, causing shivering – both of which warm us up. As a result, the body's temperature starts to rise, slowing down the ability of viruses to multiply.

→ Page 12 has more on the fever response

Cytokines also trigger more localised heat and swelling, by increasing blood flow to the affected area and alerting the rest of the immune system to prepare for a fight. The blood vessels become more permeable, allowing fluid and white blood cells to leak out and flood the tissue. These cells then attack and gobble up any invading pathogens, and later clear up the debris.

This basic inflammatory response comes in different flavours, depending on what challenge the body is facing. If you sprain your ankle, for example, the joint swells and becomes hot, painful and difficult to move. If you have a cold, it is the blood vessels in the airways that swell, blocking the nose while inflammatory histamines stimulate mucus production, which in turn sets off coughs and sneezes. If you have flu, you get all of this, plus inflammation spreads throughout the body, causing joints and muscles to ache.



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Cytokines trigger inflammation as part of the body's immune response

When cytokines make their way to the brain, which has a separate immune system to the rest of the body, divided by the blood-brain barrier, they trigger macrophage-like cells in the brain called microglia to secrete further cytokines to bring about "sickness behaviours": low mood, loss of appetite and lethargy.

Sometimes our immune responses can kill us. When SARS-CoV-2 – the virus behind the covid-19 pandemic – enters the lungs, the innate immune system kicks in, attracting other immune cells to the region to attack the virus, resulting in localised inflammation. But in some patients, excessive or uncontrolled levels of cytokines are released, which then activate more immune cells, resulting in hyperinflammation. As well as targeting the invading organism, this "cytokine storm" attacks the body's organs and tissues, resulting in organ damage and sometimes death. This also happens in sepsis, or blood poisoning, which is often triggered by a bacterial infection spilling into the blood. Cytokine storms also occur with some non-infectious diseases, such as multiple sclerosis and pancreatitis.

Of course, not everyone responds to infections in the same way. When the Covid-19 pandemic struck in early 2020, It quickly became clear that older people, and those with certain underlying health conditions such as diabetes and cancer were at higher risk, although even within these groups the threat it poses to individuals varies dramatically. It can also kill young and otherwise healthy individuals, whereas others experience no symptoms whatsoever. The same is true of many other infections.

To understand why this is so, we need to look closely at not just the infectious agents, but ourselves. The first factor which influences our immune responses is age. But when it comes to immune health, it has become clear that age is just a number. Some 60-year-olds have the immune system of a 40-year-old, whereas others are more like an 80-year-old.

→
For more on biological versus chronological age, see page 40

If you are younger than 60, in good health and don't have too many bad habits, then your immune system is probably functioning pretty well. However, as we age, our immune systems gradually deteriorate, and the more likely we are to get seriously ill or die because of it. This "immunosenescence" starts to affect people's health at about 60, and becomes more pronounced as time goes on.

During a typical winter flu season, for example, very few people under the age of 65 get ill enough to be hospitalised. About 20 per cent of those aged 65 to 74 who catch the disease do, although hardly any of them die. But among the over 75s, about half of those with flu end up in hospital and 30 to 40 per cent of them die. Most of those who pull through never fully recover. Similar hospitalisation and mortality rates are being seen with SARS CoV-2.

To many, this immunosenescence may sound like a far-off threat, but it is something that should concern us all. The decline can start surprisingly early in life, during puberty, and be accelerated by all kinds of lifestyle factors. People who smoke or who are obese are particularly likely to have an immune ›

> “Like a lot of things in life, immune strength is a genetic lottery”

system that is older than their chronological years. Being sedentary is another risk factor.

Even among people with a fully functioning immune system there are significant differences in how well it works. In 2018, the Milieu Intérieur Consortium based at the Pasteur Institute in France scrutinised circulating immune cells from 1000 men and women aged between 20 and 69. They found major individual differences between people of different ages, but they also discovered that people of the same age can have very different immune systems.

This is partly down to varying lifetime exposure to viruses and bacteria, which can radically alter the composition of your adaptive immune system – the wing of your defences that produces antibodies targeted to attack threats. For instance, the immune age of children living in Bangladesh, who generally have a heavy burden of infectious diseases and parasites, appears similar to that of young adults in California, undermining the adage that “what doesn’t kill you only makes you stronger”.

That said, an underworked immune system also seems to be problematic: people who aren’t exposed to infections and parasites in childhood seem more susceptible to autoimmune disorders such as allergies later in life.

Genetics is also key. The Pasteur team found big disparities in the composition of people’s innate immune systems, the generalised first line of defence, and these mapped onto differences in their genes. The significance of these genetic variations in immune response isn’t yet known, but it may be that some people are naturally better than others at dealing with certain threats. Like a lot of things in life, immune strength is a genetic lottery.

Take HIV, the virus that can lead to AIDS. In the mid-1990s, teams in New York and Boston discovered that certain individuals somehow avoided infection with HIV, despite multiple exposures via sharing needles to inject drugs or by having unprotected sex with infected partners. It turned out that people carrying certain mutations in a gene called CCR5 were completely resistant to HIV.

The CCR5 protein wedges itself into the outer membrane of immune cells called T-cells and acts as a lock that HIV must pick to enter. People with some mutations of the gene that codes for this protein had unpickable locks. This discovery, published in 1996, was a breakthrough in understanding how HIV enters cells, and directed us to potent new approaches for antiviral treatments.

A similar approach has been taken with hepatitis C. Most people who contract the hepatitis C virus (HCV) will develop chronic infection, but about a quarter somehow clear the virus. Several genetic variations have now been identified, which affect whether someone can clear HCV without pharmaceutical help, and how likely they are to respond to antiviral therapy.

Our genes don’t just influence our vulnerability to viruses, but to bacterial infections too. Consider *Streptococcus pneumoniae*. Pulmonologist Stephen Chapman at the University of Oxford has seen plenty of people hospitalised with pneumonia caused by infection with this bacterium, but one in 15 healthy

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CORONAVIRUS

GET THE LOWDOWN ON THE
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HOW TO STOP IT SPREADING /
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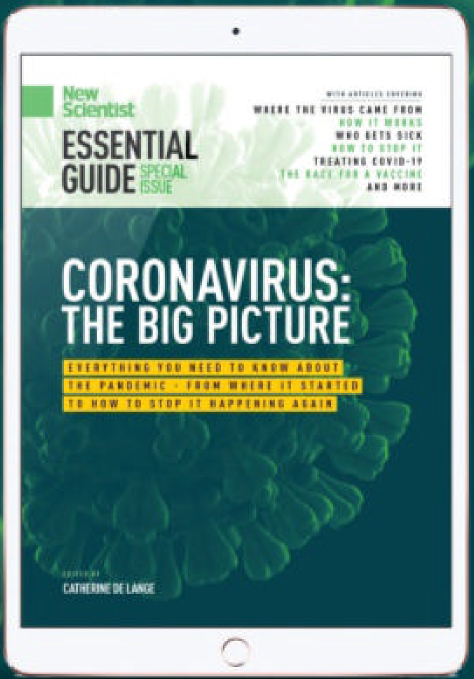

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ESSENTIAL GUIDE SPECIAL ISSUE

WITH ARTICLES COVERING
WHERE THE VIRUS CAME FROM
HOW IT WORKS
WHO GETS SICK
HOW TO STOP IT
TREATING COVID-19
THE RACE FOR A VACCINE
AND MORE

CORONAVIRUS: THE BIG PICTURE

EVERYTHING YOU NEED TO KNOW ABOUT
THE PANDEMIC – FROM WHERE IT STARTED
TO HOW TO STOP IT HAPPENING AGAIN

EDITED BY
CATHERINE DE LANGE

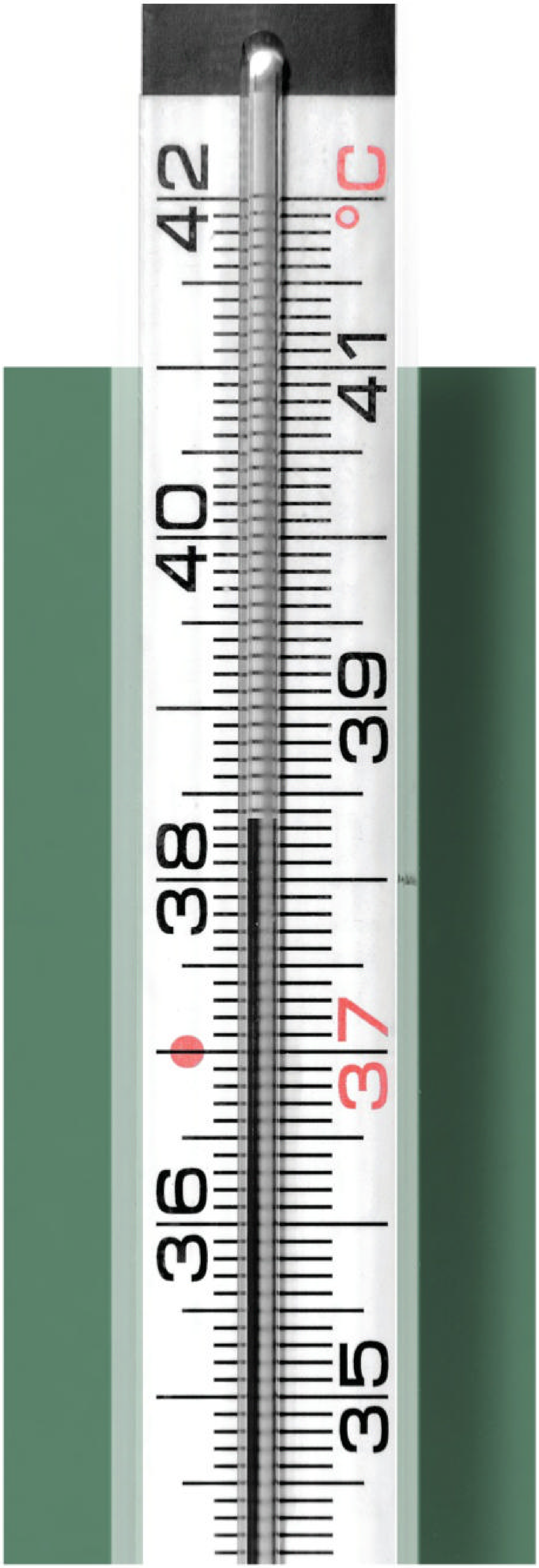
adults in the UK carry the microbe harmlessly in their respiratory tracts. In his efforts to understand why, Chapman has identified several gene variants associated with immune function that influence whether these bacteria cause people harm.

Then there's gender. When epidemiologists began to examine statistics about who had been hospitalised by covid-19 and who had died, they noticed that men seem worse affected. One recent analysis of data from several European countries found that they were more than twice as likely to be infected with the new coronavirus, while a study from China found that men had 1.7 times the risk of death. A similar trend was identified in 2003 during the outbreak of SARS, a disease caused by a related coronavirus.

Some of this may be down to the effect of the hormone oestrogen on our immune systems. Researchers at the University of Iowa have found that male mice – and females that can't produce oestrogen – are more likely to die after infection with the SARS coronavirus. Other researchers have hypothesised that oestrogen promotes a more vigorous immune response, which gives individuals who produce more of the hormone an advantage when fighting disease. The trade-off is that it may also put them at risk of autoimmune conditions such as multiple sclerosis, which disproportionately affects women.

As we come to better understand how our genes and hormones contribute to the severity of disease, another major challenge will be to work out how these interact with environmental factors such as smoking, exposure to pollution, the impact of crowded living spaces and many other things. As more and more of these findings come out, the influence that our individual genes and circumstances can have on our risk for infection and disease severity will become ever clearer.

The hope is that in the not-too-distant future, we will be able to learn more about the people who don't succumb to illnesses like covid-19. In so doing, we may learn how better to protect those that do. ▮



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WHY FEVER IS OUR FRIEND

As news about coronavirus spread around the world, paracetamol soon began to disappear from shop shelves as people stocked up. That probably comes as little surprise given that one of the most unpleasant symptoms of the infection is a fever, and paracetamol is one of our most effective drugs to treat it. But should we be so hasty to get our temperature down?

HUMAN body temperature is generally thought of as 37°C, although anything between 36.5°C and 37.5°C is generally considered normal. However, once your temperature hits 38°C, you have officially got a fever.

If body temperature rises too far, it can be fatal. Our cells begin to die, releasing proteins into the blood that can damage the kidneys and other organs, resulting in their failure. The exact temperature this happens at probably depends on the source of a person's fever, as well as other factors such as how hydrated they are. "The number 40 [degrees] scares a lot of doctors," says Mark Peters at the UCL Great Ormond Street Institute of Child Health in London.

So, if fever can kill us, why does it happen? Fever-like responses are observed in many organisms, suggesting its evolutionary origins may stretch back hundreds of millions of years. Even some plants have been shown to increase their leaf temperature in response to fungal infections, while cold-blooded creatures will deliberately raise their body temperature if they have an infection, by sitting on a hot rock, for instance.

Bacteria and viruses find it easier to replicate and infect cells at temperatures below 37°C, so by raising our body temperature, we may inhibit their growth. The immune system also works more efficiently when the body gets hotter. Immune cells that act as first responders to infection, such as dendritic cells, macrophages and neutrophils, have been shown to arrive at the scene faster and have an improved capacity to engulf and destroy infectious agents at 38°C to 40°C.

Fever also seems to make these cells better at recruiting and activating T-cells, which coordinate longer-term "adaptive" immune responses, such as antibody production. And T-cells and antibody-producing B-cells also better respond to instructions from the immune system at these temperatures.

All of this raises the question of when – and how – fever should be treated. Running a fever feels unpleasant, and we are often advised to take medication, such as paracetamol or ibuprofen, to bring our temperatures down.

On the other hand, children with the common viral infection chickenpox have been shown to recover faster if they are left to run a mild fever, compared with those given fever-reducing drugs. Similarly, people who are admitted to intensive care units with infections and a slightly raised temperature tend to fare better than those who have a normal temperature, or one higher than 40°C.

Most experts agree that very high temperatures require treatment, but in adults, a mild fever of up to 38.9°C, in the absence of more worrying symptoms, will probably get better with rest and fluids. So, if your fever is mild, and you aren't in great discomfort, you might want to remember what is going on inside. While you should always seek urgent medical attention if things are getting too hot, permitting a mild fever is likely to allow your immune systems to do its job – as it has been designed by millions of years of evolution – better. ∎

BEYOND ANTIBIOTICS

So far we've encountered bacteria mainly as foreign agents out to infect us. But there are some 10,000 species of bacteria in our bodies, 99 per cent of them harmless. They help furnish us with nutrients, tune our immune systems, balance our metabolisms and possibly even ward off mood disorders. And as anyone who's had an upset stomach after taking antibiotics can attest, when we target the dangerous minority of disease-causing species, we often wind up killing off the good ones too – while creating antibiotic-resistant versions of the ones we seek to destroy. There could be a better way.

IN THE latter part of the 19th century, mounting evidence that germs cause disease kicked off more than a century of war against them. We expunged them from our water, food and homes with disinfectants, roused our immune systems against them with vaccines and wiped out bacteria with penicillin and other chemical weapons. Human deaths caused by infectious diseases fell by more than 90 per cent, contributing to a broader transformation of society. If nothing else, the arrival of coronavirus is a reminder of the extent to which we have rid ourselves of infectious disease and the plagues which have long been a feature of human history.

This freedom has come at a cost. Taking a dose of antibiotics is like throwing a stink bomb into a subway. The criminals clear out, but so do the citizens: the beneficial bacteria, numbering some 10,000 species, with which we share our body space and on which we rely on for good health.

Meanwhile often the rats and cockroaches remain, unfazed by the stench. And the survivors can become resistant to our weapons. Every year, 23,000 people in the US alone die from antibiotic-resistant infections. Proclamations of an impending superbug apocalypse are overblown, as these bugs primarily attack older people and those who are already ill. But it is clear that overusing antibiotics drives up resistance, and we are running worryingly low on replacements.

If we were to treat infections without killing bacteria, they wouldn't need to evolve resistance to our antibiotics. Not only could this strategy, known as anti-virulence therapy, provide alternative drugs to fight infection, it could also help preserve potent

DIMITRIS66/ISTOCK PHOTO

antibiotics for when we really need them.

To achieve this, we need to stop bacteria behaving badly, and from sticking around in the places they aren't wanted. If unwanted bacteria can't latch onto our tissues, they can't invade. This strategy has already shown promise for treating urinary tract infections (UTIs), which are particularly common in women. Most UTIs are caused by *Escherichia coli*, which use their hair-like pili to bind to carbohydrates on cell surfaces. But now researchers have found that if you give people carbohydrates similar to those naturally found on cells, they act as decoys. *E. coli* bind to the decoys and fail to get a grip on the cell surfaces. As a result, the bacteria get flushed out when people urinate.

In a small trial of women with recurrent UTIs, just 15 per cent of those given the simple carbohydrate D-mannose got a UTI within six months, compared with 20 per cent of those treated with antibiotics and 61 per cent of the women given a placebo. In another trial, women who drank a solution of D-mannose didn't get another UTI for more than six months, on average, compared with 52 days for those given antibiotics.

Daniele Porru and colleagues at the San Matteo Foundation in Pavia, Italy, who ran the trial, also found that antibiotics became more potent for the women treated with D-mannose instead. Because antibiotic-resistant bacteria are generally less fit than susceptible strains, in the absence of antibiotics, regular bugs beat out resistant ones for resources, and come to outnumber them. That means when you do need antibiotics, they are more likely to work as most of the bacteria are the vulnerable kind. When the researchers tested samples of the bacteria, they noted an increased sensitivity to antibiotics, and very few side effects.

More advanced blockers are in the works too. Scott Hultgren and Jim Janetka at Washington University in St Louis have developed synthetic mannose derivatives that may be more effective and linger longer within the body, meaning you need less to make a difference. Studies in mice show that a single dose can prevent *E. coli* infections for at least three days, and begin to clear existing infections within 6 hours. And by blocking *E. coli* instead of blasting them with antibiotics, the bacteria didn't need to evolve resistance to drugs, and beneficial bacteria living in the urinary tract were left unharmed. The potential impact is big: in the US alone, more than 25 million antibiotic prescriptions are written for UTIs each year, and up to half of the people who take them will have a recurrence.

If you can't stop bacteria from sticking, the next line of defence is a long-forgotten treatment. The idea is to neutralise the toxins that bacteria produce to break open cells and gobble up nutrients. It is a strategy first used in the 1880s by German bacteriologist Emil von Behring and his Japanese colleague Kitasato Shibasaburo. The pair injected sublethal doses of diphtheria and tetanus toxins into animals, harvested the toxin-neutralising antibodies they produced, and then used these to treat patients. This strategy eventually halved the death rate from diphtheria and tetanus, and earned von Behring the very first Nobel prize in medicine. But when antibiotics came along, anti-toxin therapy was largely abandoned. With the rise of antibiotic resistance, it is now getting a fresh look.

One area in which anti-toxins have huge potential is in treating diarrhoea. Each year nearly 30,000 people in the US die from diarrhoea caused by *Clostridium* ›

> **“Taking a dose of antibiotics is like throwing a stinkbomb into a subway”**

difficile, an infection often acquired after antibiotic treatment during hospital stays. The solution is usually even more antibiotics, but for a quarter of patients, the infection comes back. In a recent trial, when people were also given a drug that neutralises *C. difficile* toxins, it nearly halved the recurrence rate.

The trouble is, this kind of therapy doesn’t necessarily reduce risk of death from this infection down the line. There is reason to hope that the next generation anti-toxin drugs will cover more strains of bacteria and be more effective: a lab-grown antibody to toxins produced by the common bacterium *Staphylococcus aureus* – known as MRSA in its antibiotic-resistant forms – can prevent death and disease in infected mice. It is now being tested to prevent pneumonia caused by *S. aureus* in people on ventilators.

Another approach is to play with the relationship between dangerous bugs and our immune systems. This is tricky, however. We have evolved together with bacteria in a game of cat and mouse that is millions of years old. The bacteria hide; our immune cells evolve to seek out and destroy them; bacteria evolve new ways of hiding. *S. aureus*, for instance, can cloak itself in human proteins, rendering it invisible to an immune system trained to ignore the body’s own cells.

There is research into stripping away such disguises, but the more promising strategy is perhaps surprising: hide the bacteria on purpose. As we saw earlier in this chapter, some of the most devastating consequences of infection – particularly septic shock, which kills more people in US hospitals than cancer – are not caused by the infection itself, but an overstimulated immune system on a rampage.

One component of the cell walls of many harmful bacteria is a molecule called endotoxin. Its presence sets off an alarm triggering our immune systems to react. But despite its menacing name, endotoxin itself does no damage to our cells. Indeed, mice without the necessary gene to detect it are less likely to die from infection (though they are more likely to get infections in the first place). In studies, multi-drug resistant *Acinetobacter* kills all infected mice by driving them into septic shock. But when infected mice are given the experimental drug LpxC-1, which blocks the production of endotoxin, the death rate plummets. Because bacteria signal their presence in many other ways that prompt a less severe response than endotoxin, mouse immune systems eventually fight off the infections, but without setting off the alarms that send the animals into shock. Human trials may begin in the next few years.

Another strategy for thwarting harmful bacteria rather than wiping them out is to break up their social networks. For many kinds of bacteria, the decision to switch from peaceful grazers to aggressive predators is a communal one. The process is set in motion by so-called quorum-sensing genes, which only kick into action when there are enough relatives around. If the signals from these genes can be scrambled, the bacteria won’t attack.

This approach is appealing because it works on a more global scale. In principle, a single quorum-sensing inhibitor could prevent many types of bacteria from producing a whole menu of toxins. And studies in mice show that the strategy works. The trouble is, if the ploy were too effective, it could backfire: bugs that are resistant to these quorum-sensing scramblers could be more likely to survive and cause harm. Such drugs could inadvertently select new strains of superbugs which pump out high levels of toxins continually.

It is still years away from human trials, but there may be a less risky way to achieve the same thing. Some of the harmless bacteria that live on us also get a say in whether bad bugs go on the attack. One theory suggests that their presence deters harmful bacteria from invading because they don't want to share their plunder with strangers. For example, *Corynebacterium*, a common skin inhabitant, releases compounds that suppress *S. aureus* infections in mice. Not only do they throttle production of *S. aureus* toxins, but they turn up the expression of genes associated with a non-infectious lifestyle. They don't just disarm *S. aureus*, they convert it to a pacifist.

The golden age of antibiotics is over. We will never again develop safe, cheap, effective new ones as fast as bugs develop resistance to them. But old habits will be hard to break. Antibiotics have saved millions of lives. Even in our current age of resistance, most first-line treatments work most of the time. That means these new strategies have to clear a very high bar before doctors take them seriously. None of these strategies is a silver bullet. But they may provide alternatives, help make existing antibiotics more effective, and crucially, leave us less susceptible to disease.

If we don't reassess our use of antibiotics, we may have traded freedom from bacterial plagues for death by a host of other ailments. Obesity, fatty liver disease, diabetes, arthritis, inflammatory bowel disease, multiple sclerosis, asthma, anxiety and depression have all been linked to use and overuse of antibiotics (see "Are antibiotics making us sick?", left). Without the ability to fight off infections, modern life would be impossible, but we also need to preserve the microbial communities so crucial to our health and well-being. It's time we learned to get along.

ARE ANTIBIOTICS MAKING US SICK?

Antibiotics are widely regarded as some of the safest drugs going. Indeed, until recently many doctors prescribed them for viral infections – despite knowing they were useless – on the grounds that "it can't hurt".

Except that it can. And not just because it leads bacteria to develop resistance to the drugs. Antibiotic-associated diarrhoea and allergic reactions commonly send people to hospital. And antibiotic use is almost always the cause of diarrhoea associated with *Clostridium difficile*, which kills nearly 30,000 Americans every year.

People who study the microbiome believe the toll may be far higher. One study in Denmark, for example, revealed that people who redeemed five or more antibiotic prescriptions over the course of a 15-year period were much more likely to develop type 2 diabetes compared with those who took antibiotics once or less during this time.

Beyond diabetes, changes in the balance of bacteria in our guts are now associated with obesity, inflammatory and autoimmune disorders and even depression. Antibiotic use, especially in childhood, has been found to be a risk factor for all of these.

The link to obesity shouldn't necessarily surprise us: antibiotics have been used to fatten livestock since the 1940s. The first study showing a similar effect in people dates to 1955. But the mechanism was a mystery and there was little interest in follow-up. Germs were our enemy, antibiotics got rid of germs, so antibiotics were good, right?

There is a lot that we still don't know about the balance of bacteria in our bodies, but we now know enough to understand that constantly disrupting it is imprudent, even dangerous. Even if the rise of antibiotic resistance did not drive a need for alternative therapies, the need to preserve our health does.

HAVE WE BECOME TOO CLEAN?

The surest way to stay healthy is to avoid getting infected in the first place. That means hygiene. In the wake of the coronavirus pandemic, we have got used to regularly washing our hands and sneezing into our elbows, and even the widespread wearing of face masks in public. But supermarket shelves packed with antibacterial and antiviral cleaning agents bring with them whispers about these products' effects on beneficial bacteria. Might their overuse be harming us, and even fuelling antibiotic resistance?

"I HATE housework. You make the beds, wash the dishes and then six months later you have to start all over again". Adherents of this Joan Rivers quote got a fillip back in 1989, when David Strachan, then an epidemiologist at the London School of Hygiene and Tropical Medicine, proposed his hygiene hypothesis. He suggested that modern lifestyles, with their lack of unhygienic exposure, mean we catch fewer infections in early childhood, and that this predisposes us to developing allergies.

Some of the evidence is fascinating. Children who grow up on farms seem to be healthier, as are children whose parents wash dishes by hand rather than using a dishwasher, and those who have a dog. Meanwhile, a 2014 paper found that children are less likely to develop precursors to asthma if, during their first year, they're exposed to particles from cats, mice and cockroaches.

Many of us have embraced the idea of a link between a little bit of dirt and good health. There's just one problem: things probably aren't that simple. In recent years, thousands of studies have linked changes in the microorganisms living inside our bodies to everything from allergies and asthma to obesity, depression, and Alzheimer's disease. This emerging understanding of what's known as our microbiome suggests that, rather than there being a clear distinction between "clean" and "dirty", we have a complicated relationship with

YANA TATEVOSIAN/ISTOCK PHOTO

bacteria. Being exposed to some kinds is good for us, to others not. And figuring out which is which isn't easy.

One thing is becoming clear, however: it's diversity that counts. A 2015 study of nearly 400 infants in Germany hinted as much, when researchers found no direct link between their chances of developing asthma or allergies and their caregivers' personal and home cleanliness. What did make the difference was their exposure to bacteria. Several studies show that healthier people tend to host a wider range of microbes. Western lifestyles may have adverse effects on this diversity, which was found to be 40 per cent lower than that detected in an isolated, traditional hunter-gatherer society. And a 2013 study found that infants whose parents picked their dropped dummy up off the street, sucked it clean, and then handed it back to their child, were less likely to develop asthma or eczema. The organisms in their saliva were also different from the ones inhabiting infants whose parents would never do such a thing, prompting the researchers to suggest that the protective effect is down to the transfer of beneficial microbes from parent to child.

There is now also evidence for why living on a farm is so good at reducing allergies – the bacterial components in farm dust suppress inflammatory immune responses. This seems to indicate that the hygiene hypothesis is in need of revision. Possibly it is not so much infections as exposure to a wide variety of bacteria that benefits our immune systems.

When we are exposed to these beneficial microbes is also crucial. The most important time seems to be early childhood. According to current thinking, the cut-off may be as early as three. So, if you're the parent of a very young child, it is probably very important to take them outdoors and let them play on the ground.

By the time we are adults, our microbiome may be largely set, so any suggestions that shirking the chores – or your personal hygiene – could improve your health, is spurious, and potentially even harmful.

For example, there are about 17 million cases of food poisoning a year in the UK, caused by microbes including *Norovirus* and *Campylobacter*. Many cases are picked up in restaurants, but a study of 18 European countries suggests that nearly a third of food-borne outbreaks occur inside our own homes.

Filth has consequences. About 50 per cent of chickens in the UK carry *Campylobacter*, the country's most common cause of food poisoning, and the bacteria can easily transfer from the raw meat to your hands or a chopping board. Seen in this light, anything that encourages people to cut back on habits like handwashing is dangerous.

But while being too slovenly stands a good chance of giving us diarrhoea, in certain respects it seems we don't need to be too clean. In particular, you might want to cut back on antibacterial handwashes and laundry detergents. Not only might some of these have less benefit than advertised, but there is some › evidence they might contribute to bacteria becoming resistant to antibacterials and even antibiotics. There's also growing concern about indoor pollution connected with overzealous use of certain household products.

How do we find the sweet spot between being too dirty and too clean? "Targeted hygiene" could be the answer. Although this strategy has been around since the 1950s, it was largely limited to hospitals and industries such as catering, pharmaceuticals, and cosmetics. Increasingly though, hygiene experts believe it should become an everyday feature of people's lives.

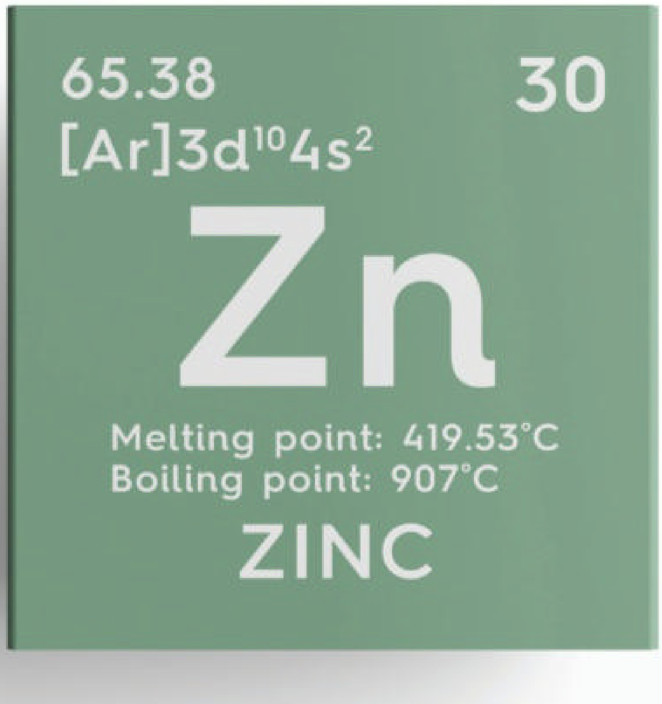
Rather than striving for a sterile home or office, targeted hygiene means focusing only on removing harmful bacteria, from important surfaces, at critical times. Most of the cleaning should focus on doorknobs, light switches and the bathroom – anything we touch a lot. It's also crucial to thoroughly clean everything you use while cooking. That includes all surfaces, chopping boards and utensils that come into contact with raw meat, as well as unwashed dirty vegetables, whose bacteria can give you food poisoning just as raw chicken can. The most important advice is to wash your hands, after cooking, before eating and after using the toilet.

But beyond that? Well, Joan Rivers fans can take heart: cleaning the walls, floors or the furniture really can wait six months. If you're not allergic to dust mites, vacuuming is entirely optional. And you can forget about making the bed – especially if you're allergic to dust mites. Mites need a humid atmosphere to survive, so leaving the covers open in the morning might help to kill the beasts.

Beyond these basics, it seems there is one big thing we can do to improve our health beyond worrying too much about the state of our homes: spend more time outdoors. Preliminary findings hint that spending more time doing social sports and other outdoor activities can help restore a healthily diverse microbiome. The best advice is quite pleasingly wholesome and old-fashioned. Use cleaning products sparingly, in the places that matter, open the windows after you've finished, and then go out for a nice long walk in the fresh air. ∎

IMMUNE BOOSTERS

As we've seen, many of the factors affecting our immune system's performance are out of our control. But beyond cleaning regimes, there are some things we have more control over. Some dietary supplements can work – although they're probably not the best medicine



NUMEROUS dietary supplements are sold for their supposed immune-boosting powers. Many of these health claims are spurious, stemming from tests in petri dishes, rather than from randomised, controlled trials in people – the gold-standard for any scientifically proven effect. But it's not all marketing guff.

Of commonly sold supplements, zinc probably comes out best, with evidence that it can both prevent colds and shorten their duration if started within 24 hours of the symptoms first appearing. It is thought to work by stopping the cold virus from replicating, or preventing it from gaining entry to cells lining the airways. Even so, overdosing on zinc will suppress your immune system, so care is needed.

Vitamin E has also been shown to enhance immune function in human and animal studies. Dayong Wu at Tufts University in Boston and his colleagues tested vitamin E in older people – giving half of the 670 residents of a nursing home a small daily dose of vitamin E and the other half a placebo – and found significant differences in the rate of upper respiratory infections. A bigger clinical trial is in the pipeline, but the evidence is already strong enough that Wu recommends people over 65 routinely take 200 international units (IUs) of vitamin E. Moderation is again key, as vitamin E can be toxic in high doses.

Vitamin D, meanwhile, appears to do something similar for the innate arm of the immune system, especially among people living at latitudes where there isn't enough winter sunlight for their skin to synthesise the molecule. A 2017 review of the evidence for taking vitamin D supplements concluded that it helps prevent upper respiratory tract infections. About 1000 to 2000 IUs should be safe and beneficial, says Wu, but people shouldn't go higher than that because, once more, big doses actually suppress T-cell function.

SANCHES812/ISTOCK PHOTO

But maybe popping pills isn't the best approach. Exercise is a proven immune-boosting strategy. It keeps the thymus youthful, the heart-shaped patch of lymphatic tissue, located beneath your breastbone, where new T-cells mature before being released on active duty. T-cells are pivotal in the adaptive immune response, the more targeted part of the system.

The thymus degenerates with age, and our T-cell count with it, with consequences for our ability to fend off new pathogens. However, when Janet Lord at the University of Birmingham, UK, and her colleagues took blood samples from 125 amateur cyclists aged between 55 and 79, many of whom had been regularly riding long distances for decades, they found that their T-cell counts were similar to those of much younger people and their thymuses were youthful.

Exercise is also good for our neutrophils, a crucial first line of defence against bacterial invaders. When bacteria are detected, neutrophils squeeze out of the blood vessel and barrel towards their target, engulfing them like Pac-Man, spraying them with deadly chemicals, or disgorging their DNA and throwing it around the invaders like a net.

The ability of neutrophils to tunnel through tissues and find their target becomes increasingly erratic as we age. Older neutrophils can still detect invaders, but often blunder haphazardly through tissue or charge off in the wrong direction. Not only does this reduce the speed and efficiency of the immune response, it can also result in friendly fire – a leading cause of the generalised low-grade inflammation that creeps throughout our bodies as we age.

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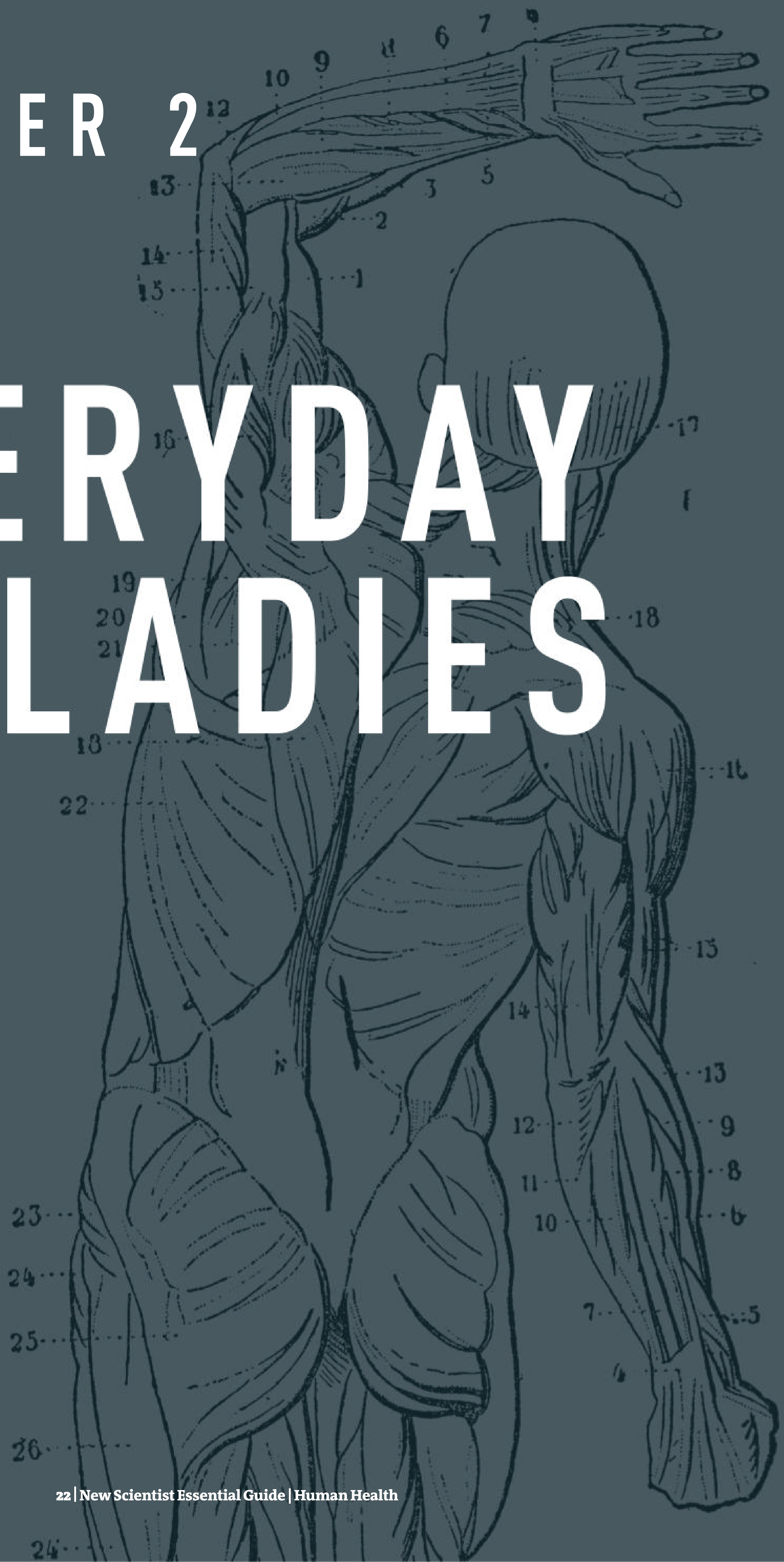
For more on inflammation and ageing, see page 44

In a separate study, Lord and her colleagues measured exercise levels and neutrophil migration in 211 older adults, and found that those doing 10,000 steps a day on average had neutrophils as good as those of young adults. Neutrophils don't kill viruses, so they won't prevent you from catching diseases like covid-19 or influenza, but they will shore up your defences against bacteria – including helping to protect against secondary infections, such as bacterial pneumonia. ▮

CHAPTER 2

EVERYDAY MALADIES



Modern life seems to throw all sorts of novel health challenges at us, be it ubiquitous stress or the rise of allergies and food intolerances. But there are few things new under the sun. Stress derives from an essential evolutionary response that allows us to survive in a fast-changing world, while allergies represent just another misdirected immune response.

Understanding the origins of these conditions allows us to combat them better. The answers are often the same: more exercise, better diet and a good dose of social interaction.

WHAT STRESS IS ALL ABOUT

Whether you're running late for a meeting, or coping with a personal loss, stress is an unavoidable part of modern life. Yet, while some people seem to float along unfazed by the stressors that life throws at them, others are overwhelmed and sink. Understanding the key to this resilience wouldn't just help us to manage life's daily struggles better, it might also teach us how to use stress to our advantage.

STRESS is an essential physiological response that allows us to quickly adapt to the world around us. It begins in a region of the brain called the amygdala, which is on constant surveillance for any potential threat. The amygdala combines sensory information with memories of similar situations to judge whether an emergency response is required. If alarm bells ring, a distress signal is sent to the hypothalamus – a small nodule near the base of the brain – which activates two major pathways. The first triggers our ancient fight-or-flight system, which pumps out adrenaline, making us more alert by increasing our heartbeat and the efficiency of our breathing and forcing more blood into our muscles. The second prompts the release of other hormones, including cortisol. This keeps the stress response active and releases stored glucose to give us more energy. It also suppresses our digestion, immune system and inflammation, to focus resources on the immediate threat. When the threat has passed, cortisol levels drop, helping to bring all these chemicals back to their original levels.

This is all very handy when you are facing a poisonous snake or an oncoming vehicle, because it enables you to start taking evasive action before

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DANIEL STOLLE

you have even registered the threat. It also allows you to concentrate on your work as a deadline looms or focuses your thoughts when speaking in front of an audience. But sometimes the stress response kicks in unnecessarily or is so powerful it consumes us.

In 2018, the largest known study of stress levels in the UK showed that three-quarters of people had been so stressed in the past year that they had felt overwhelmed or unable to cope. It can be so damaging to our well-being that one in three of these people had been left feeling suicidal, and one in six had self-harmed.

Sudden or severe stress can result in PTSD and depression. And low-level, chronic stress creates a slew of other health problems. With no let up, raised levels of adrenaline can damage blood vessels and increase the risk of heart attack and stroke. Cortisol can cause digestive problems, weight gain and diabetes. And constant modulation of the immune system can lead to fatigue and physical and mental health issues.

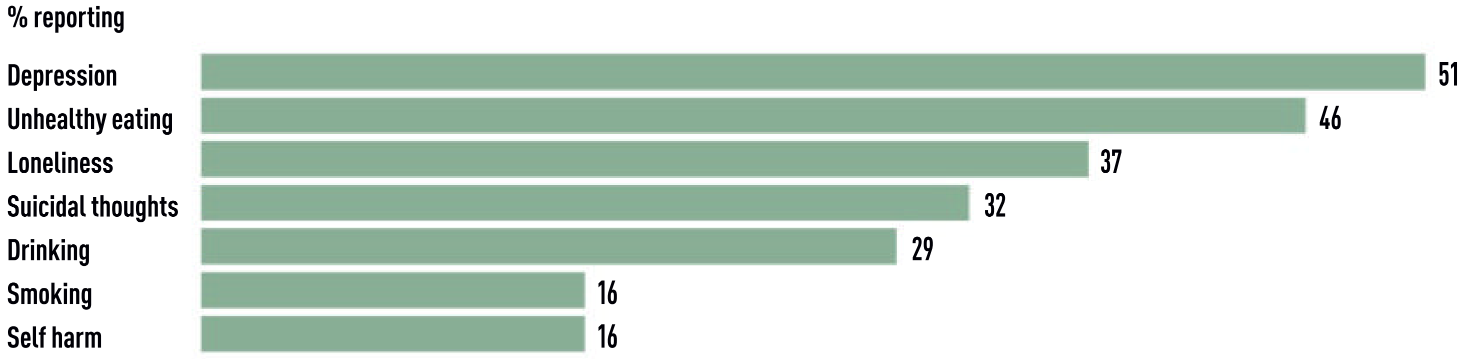
Whether stress has positive or negative consequences often depends on how we deal with it. Your reaction to stress and how quickly you return to normal when the stressor has passed is called resilience. This is what varies significantly between individuals. But what makes some of us so resilient while others struggle to cope?

Upbringing plays a part. Animal experiments demonstrate that early trauma affects an individual's response to stress as an adult. Testing this link in humans is difficult, though, given the diversity, frequency and severity of events that can negatively impact a child. One of the few studies to give an insight is the Bucharest Early Intervention Project, a one-of-a-kind study of children raised in Romanian orphanages. In total, 136 children were randomly chosen from six institutions, half of whom were fostered between the ages of 6 months and 30 months. When the children were around 12 years old, a team led by Katie McLaughlin at the University of Washington, Seattle, assessed their response to stress-inducing tasks. Analysis of their saliva revealed that those who had been fostered had similar cortisol levels to a control group of children living in nearby families – but only if they had been placed in foster care before the age of 2. Those fostered later or who remained in orphanages had a blunted stress response, producing less cortisol.

This might seem like a good thing because it suggests that these children were less easily stressed. In fact, it seems to be a manifestation of underlying damage to the normal stress response, which is associated with long-term behavioural problems and an increased risk of depression. Other research hints at what is going on. The first two years of life are a sensitive period in which our environment is particularly likely to cause changes to the brain that influence the stress response. The mechanisms are probably numerous, but research led by Linda Chao at the University of California, San Francisco, suggests that trauma can trigger an increase in myelin in the brain's grey matter, where the cell bodies of neurons are found. Myelin normally forms an insulating sheath around nerve fibres, but in grey matter it prevents new connections forming between neurons and is linked with PTSD and depression.

STRESSED OUT

An online poll of 4619 people in the UK found that 74 per cent had been overwhelmed by stress in the past year, and that stress had a variety of negative repercussions in their lifetimes



SOURCE: MENTAL HEALTH FOUNDATION

As for which aspects of the early environment are key to healthy development, experiments point to social interaction, stimulation and parental support. Developmental psychologist Suniya Luthar at Arizona State University identifies the single most important factor in developing stress resilience as a strong, supportive, dependable relationship with your primary caregivers. However, adults who did not have a good childhood experience are by no means doomed, she says: "If they are able to find the same ingredients – dependable, supportive, close relationships – the ill effects of childhood adversity can certainly be reduced."

An individual's ability to cope with stress isn't purely down to early life experiences. Genes also play a role, especially those involved in the production of a chemical called neuropeptide Y (NPY). Exactly how this works is unknown, but animal experiments suggest that NPY acts as a kind of on-off switch for the stress response. Faced with a threat, production soars, helping to instigate a rapid response, but levels quickly return to normal once the danger is over (see "Could we vaccinate people against stress?", overleaf).

To assess NPY's role in humans, studies often focus on members of elite military forces who perform well under extreme stress. For example, researchers at the US National Center for PTSD in Connecticut compared blood samples from US special forces and regular soldiers during a training exercise at Fort Bragg in North Carolina, where they were deprived of food and sleep, pursued by the "enemy" and interrogated when caught. This revealed that the special forces soldiers sustained higher levels of NPY for longer during the exercise. Their NPY also returned to its original level more quickly afterwards, showing that they were better able to recover from the stress they had experienced. In addition, the more NPY an individual released, the less confusion and fewer mental health issues they reported during the training.

We all inherit different variations of NPY genes. Some protect against stress, while others increase the risk of an impaired stress response and the psychiatric conditions related to this. So perhaps these special forces soldiers hit the genetic jackpot. However, there are tantalising hints that we aren't stuck with the NPY that our genes dictate. For instance, after a surprise simulated ambush, the NPY levels of marines who had previously completed an eight-week course on mindfulness returned to normal far quicker than those of soldiers without such training.

Another common thread that links chilled-out people is to do with their personality, particularly their sense of humour. Research shows that people who see the funny side of life's mishaps are likely to interpret and react to stress more positively, buffering themselves against some of the negative effects. For instance, in a study of firefighters, Michael Sliter at Indiana University–Purdue University Indianapolis, found that, in general, the number of symptoms of PTSD and burnout they reported correlated with the number of stressful situations they had been in over the past month. But firefighters who used humour more often as a coping mechanism were less likely to experience these negative effects. ›

“There is an intimate link between gut bacteria and mood and behaviour”

Laughing releases feel-good hormones thought to make us less likely to ruminate on or re-experience stressful events. It also helps us build relationships, providing the social support that is a key to resilience. But there is good news for anyone who struggles to find their funny bone. A pilot study in Austria put 35 people who were experiencing stress, exhaustion or depressive symptoms through a seven-week “humour training” course, including role play, finding humour in everyday life, cultivating playfulness and learning how to make others laugh. The training seemed to decrease perceived stress and increase cheerfulness, although it was limited by not having a control group.

An additional factor influencing your stress resilience is more surprising. Growing evidence points to an intimate relationship between gut bacteria and our mood and behaviour. What’s more, several studies have highlighted differences between the gut bacteria in people with stress-related conditions, such as depression and PTSD, and in people without these. Stress can also make your gut more leaky, allowing bacteria to escape into your bloodstream, which triggers inflammation that can lead to physical and mental health problems. One study, for example, found that couples experiencing the chronic stress of a bad marriage had leakier guts than less hostile couples. But the relationship works in the other direction too. Mice given “good” bacteria called *Lactobacillus rhamnosus* for 28 days before facing chronic social stress were protected against some stress-induced behaviours.

Although there are still major gaps in our understanding of the complex dialogue between gut and brain, there is substantial evidence that therapies aimed at changing the balance of microbes in the gut, and also what we eat, could have an exciting role in protecting us against – even reversing – the negative consequences of stress.

All this makes it clear that people who seem immune to stress are blessed with a combination of attributes. We still don’t have a scientific way to identify the ideal stress-resilient profile, but Belgian special forces are working on it. In one study, they randomly subjected half their wannabe recruits to a highly stressful prisoner of war exercise, while the others undertook mundane weapons training. Researchers wanted to compare their hormone profiles and any deterioration of cognitive functions in later tests to gauge the effects of stress. The aim is to use these markers in future selection exercises to identify candidates likely to struggle in stressful situations. They could also be used to monitor soldiers in the field and measure the impact of training on stress resilience.

Such a resilience profile would be useful for any employer needing to recruit people for stressful jobs. But what about the rest of us just wanting to cope better when we miss a train or attend an interview? Of course, there are plenty of ways to de-stress. Regularly listening to music seems to alter many chemicals involved in our stress response, and lowers blood glucose, making challenges seem less stressful. Exercise also boosts hormones that can act to lower perceived stress. Meditation, meanwhile, has a long history as a stress reliever, and research shows that just eight weeks’ practice can trigger brain changes related to better emotional control and stress resilience that are similar to those seen in long-term meditators.

COULD WE VACCINATE PEOPLE AGAINST STRESS?

We all produce a chemical called neuropeptide Y (NPY) that acts like an on-off switch to modulate our body's stress response. Intriguingly, a single injection of NPY before a stressful experience seems to protect animals from some of the negative consequences of stress. This discovery inspired James Murrough and Dennis Charney at Mount Sinai Hospital in New York to try a similar approach for people with post-traumatic stress disorder (PTSD). Each volunteer was given an intranasal dose of NPY before reading a story designed to trigger their PTSD. Although only a small pilot study, it hinted that NPY might offer relief from some PTSD symptoms. There was a problem though: it took an hour of inhalation and a specially designed gadget to get enough of the chemical into people's brains.

For this reason, Murrough and his colleagues have turned their attention to another chemical. Infamous as a party drug, ketamine may sound like an unlikely stress buster, but it is a mainstay of modern medicine, commonly used as an anaesthetic. A version of ketamine called esketamine was also recently approved for use in treatment-resistant depression – the first new drug for depression in over 50 years.

Studies in mice have suggested that a single dose of ketamine can protect against the negative effects of chronic stress, by increasing the brain's ability to grow new neurons and form new connections. Recently, Murrough's colleague Sara Costi began the first human study to see if ketamine has potential as a human "stress vaccine". Her healthy volunteers receive one dose of ketamine – less than people tend to take for recreational purposes – or a placebo. A week later, the volunteers must give a presentation to a stern-looking panel, who provide negative feedback.

Results are expected within the year. Although it is unlikely that ketamine would ever be put in the drinking water, it could potentially be administered to soldiers about to be deployed on a mission, or to firefighters or police. Murrough acknowledges that using the stress vaccine in a non-combat scenario would be harder because stress is usually unexpected, but there might be a window of time after the stress ends, in which the drug might still be useful.

In future, we may even be able to inoculate ourselves against stress. For now, James Murrough at the Mount Sinai Hospital in New York, who is working on this, recommends good mental hygiene. Alongside regular exercise, sufficient sleep and time out to relax, you should also cultivate your friendships and social networks, as they can provide valuable support in times of crisis.

→ Chapter 4 has more on maintaining a healthy mind

But a little stress isn't necessarily a bad thing: it might just boost your cognition. A team led by Daniela Kaufer at the University of California, Berkeley, exposed rats to a stressful environment for 3 hours while tracking the development of new neurons in their hippocampus, a brain region responsible for memory. These cells proliferated more in the stressed animals than in a control group, with long-term effects. Rats that had been stressed did better in cognitive tests, even weeks later, specifically engaging their new neurons to help. We can't yet do this kind of study in humans, but we know that new neurons allow us to learn better.

It is difficult to say what the "right" amount of stress is, since it will vary between individuals. What one person finds invigorating, another may find daunting. Also, what feels stressful one day might not feel so another. If there is such a thing as beneficial stress, it is probably the difference between stress that paralyses you, and stress that you can push through and which makes you feel great afterwards, Kaufner says. You are your own best guide to this.

THE ALLERGY EXPLOSION

Faced with airline peanut bans, it is easy to dismiss allergies as imaginary modern maladies. They're not. They are a genuine immune-system reaction, and an allergic food or bee sting response can be deadly. There's even evidence that uncontrolled hay fever may progress towards more serious asthma development. So why are these conditions on the up?

IF YOUR summer months are blighted by congestion, sneezing and a runny nose, you might think your immune system has gone into overdrive, or that it is especially good at its job. But unfortunately, it's not that simple.

Allergies are caused by immune reactions to typically harmless substances in our environment, called allergens. These range from components of cat skin to certain foods.

Allergic reactions involve a special class of antibodies called immunoglobulin E (IgE), with different IgE antibodies detecting different allergens. When this happens, immune cells are triggered to release histamine and other inflammatory chemicals, leading to those nasty symptoms that under normal circumstances would be a useful defence against invading organisms.

This is a highly primed defence mechanism. IgE antibodies bind to immune cells about 1000 times more tightly than any other class of antibody. This means they are usually already attached to an immune cell, and the whole system is ready to respond as soon as an allergen is detected. This happens in seconds to minutes, while other branches of the immune system take days to respond to a cold virus, for example.

One explanation for the sensitivity of the IgE arm of our immune system is that it evolved to detect and eject what was once a common, highly aggressive threat: large, invading organisms burrowing into our skin, airways or guts. In the absence of such parasites in modern, Western lifestyles, the IgE system seems to have begun misfiring, targeting harmless chemical structures instead.

←
Turn back to chapter 1 for the lowdown on how the immune system works

The system is more amped up in some people than others, with some people having 10 to 1000 times the level of IgE in their bodies. It is possible that those who are more prone to allergies would have been better at detecting and ejecting parasites back in our evolutionary past. But being particularly prone to allergies doesn't mean your immune system is powerful or overly active in general. You are just as likely to succumb to infections as others, and there is no strong evidence that allergies make you more likely

Hay fever, or pollen allergy, may affect 30–40 per cent of people in rich nations

JANNICKE WIIK-NIELSEN/ISTOCK PHOTO

to develop autoimmune disorders, in which the immune system starts attacking the body.

People with allergies are more susceptible to asthma, however. Having hay fever, an allergy to certain types of pollen, roughly triples the risk of developing asthma. Often the same airborne allergens that trigger hay fever and pet allergies, can make someone's asthma worse. These allergies tend to be characterised by upper airway symptoms, such as a runny nose and sneezing, whereas asthma affects the lower airways, causing inflammation, muscular contraction and the production of mucus. Even so, there's a growing sense that they are different manifestations of the same disease.

They are also increasing. From 1960 to 1990, childhood asthma rose to epidemic proportions in developed nations, followed by an increase in hay fever. By 1991, the number of family doctor consultations for asthma in the UK had quadrupled in only 20 years, and appointments for conditions such as pollen and dust allergy more than doubled. Studies now suggest hay fever affects as many as 30 per cent of adults and 40 per cent of children in rich nations.

This rise in respiratory allergies was followed by a second tide. As asthma and hay fever began to stabilise in the 1990s and 2000s, food allergies in children shot up, increasing by 50 per cent in the US in just 12 years. Around 7 per cent of children in the UK and similarly developed countries now have food allergies.

It is tempting to think that these rises might be down to increased awareness and people going to see their doctor about these problems. But studies comparing different generations show this is not the case. And peanut allergies, for example, can be so severe it seems unlikely that doctors simply failed to notice them in the past.

Rapidly developing countries are now beginning to show similar increases in allergies, particularly China. Between 1990 and 2011, asthma rates in Shanghai among 3 to 7-year-olds rose from 2 to 10 per cent.

We still don't know what has caused this rise in allergies, but there are clues. Most obvious is how much Western lifestyles changed in the 20th century. According to the "hygiene hypothesis", encountered in chapter 1, allergies may be the price people in developed nations pay for massively reduced infant mortality. It proposes that allergies are more common in the modern world because children's developing ›

immune systems are exposed to fewer infections and are incorrectly trained.

Yet, this hypothesis doesn't fully add up. Major cities like London and New York had largely cleaned up their acts by 1920. Water chlorination and separate sewage made previously common infections like cholera and typhoid rare. If clean living is to blame for allergies, why did it take 40 years for asthma to begin to rise? And since 1960, developed countries have seen only minor changes in hygiene, so what has prompted the sudden and recent surge in food allergies?

Two things we know are that older siblings are more likely to get some allergies than younger siblings, and that children who grow up in big families or on farms are less likely to develop them. Rather than cleanliness in the home or exposure to infections, key factors seem to be spending time with other children and being outdoors in early life, probably because this maximises the range of microbes we meet as infants. As people in the West moved towards spending more of life indoors and in urbanised environments, as is now happening in nations like China, they may have lost contact with particular microbes that have helped hone the human immune system for millennia. This is known as the "old friends" hypothesis.

How such friendly microbes may help prevent our IgE system from misfiring is still largely unclear. But we are beginning to understand that the different bugs living in our bodies can affect many aspects of our health. It is possible that some of them help quieten down elements of the immune system, preventing any overreaction. You are unlikely to restore these missing microbes simply by neglecting your personal hygiene, however. And by the time you are an adult, there may be little you can do to shift your microbiome – it is probably too late to up sticks and move to a farm.

Yet there are still things people can do to reduce allergic symptoms, or even cure some allergies. Clinical injections of small, increasing doses of an allergen over several years can desensitise the immune system to certain allergens, including bee and wasp venom, grass and tree pollen and house dust mites. This treatment, often known as allergen immunotherapy or "allergy shots", seems to gradually build up the amount of exposure the immune system can handle. But as the technique can prompt swelling or itching near the injection site, and in some cases anaphylaxis, breathing problems and collapse, it should be administered by a clinician at a hospital.

Some experimental peanut immunotherapies have had good results in children, providing lasting effects, but patients need to keep eating peanuts to maintain the protection. Immunotherapy seems to work well for cat allergies too – but it is less effective for dog allergies. However, this isn't something you can mimic yourself by frolicking in the grass or buying a cat – in fact, doing so is likely to make the problem worse.

What about preventing them from developing in the first place? A study of nearly 6000 infants published in 2017 found that being exclusively breastfed during the first four months of life seems to be linked to a reduced chance of developing hay fever in low-risk children. But breastfeeding isn't the whole story.

Evidence is growing that, instead of avoiding allergenic foods, it may be important for high risk children – those with moderate or severe eczema, or those whose parents or siblings have allergies – to encounter them early on. Those that are introduced to peanuts between the ages of 4 months and 11 months are 81 per cent less likely to develop a peanut allergy by the time they are 5. Similarly, children who begin eating eggs at the age of 4 to 6 months are less likely to develop egg allergies.

Some guidelines in the US and Australia now recommend slowly and carefully introducing infants to potentially allergenic ingredients from the age of 4 to 6 months, although the World Health Organization still recommends giving babies nothing but breast milk until they are 6 months old.

The good news is that people can grow out of allergies – although this most likely to happen as a child. Egg, milk and soy allergies are those most often left behind, but about 20 per cent of children lose their peanut allergies. Even if they don't disappear completely, their severity can wax and wane as we age, or in response to air pollution or even alcohol. Alcoholic drinks can contain histamine, a chemical released as part of the body's immune response. This can amplify allergic reactions and boost hay fever symptoms, particularly in women.

Also, although younger women are more likely than men to report having allergies and intolerances to food, after the menopause, women no longer experience allergies at a higher rate – probably because of hormonal changes.

But if you think you have recently beaten an allergy, the chances are you have just been exposed to less of the allergen responsible: moving to a new area is the most common reason why people think they've outgrown their allergies. ▮

IF I HAVE ONE ALLERGY WILL I DEVELOP OTHERS?

Sadly, the answer is probably yes. This is in part down to basic biology: some people simply have an immune system that is more allergy-prone – probably due to a combination of genetics plus environmental exposure. Not only that, immune cells sensitised to one allergen can cross-react with other related proteins, meaning allergies can "spread". For instance, some of the proteins in birch pollen are closely related to those in alder and hazel, which peak around a month earlier, potentially prolonging the agony for someone sensitised to birch.

Foreign travel is another thing that can foster the development of new allergies. If you travel to southern Spain in spring and there is a lot of olive pollen then you could become sensitised to it. And because olive pollen cross-reacts with ash, so you might come home and find that you start getting a reaction to ash trees.

It is not just other pollens, but some foods. For example, a birch pollen allergen called Bet v 1 shares similarities with proteins in some fruits and nuts, and so people with hay fever may occasionally notice swelling and itching in their mouth when they eat uncooked fruits such as apples, peaches and kiwi. Hazelnuts, almonds or even soya milk can trigger it too.

Similarly, people with an allergy to house dust mites may find they develop reactions to crustaceans. And latex-related allergies can spread to include reactions to bananas, apples, potatoes, and tomatoes.

This is called oral allergy syndrome, and is usually harmless – but not always. One study found that oral allergy symptoms spread to other areas of the body in nearly 9 per cent of people with the condition, and progressed to anaphylactic shock in 1.7 per cent of them.

FOOD INTOLERANCES

Like allergies, the prevalence of food intolerances has risen dramatically in recent years, as has the availability and popularity of "free-from" foods. But as we understand more about which foods are causing tummy troubles for so many, the culprits are challenging much of what we thought we knew about healthy eating.

FOOD allergies and food intolerances are two different things. Whereas allergies are caused by the immune system unnecessarily responding to harmless molecules, food intolerances relate to problems digesting them. The symptoms tend to come on more slowly than those of food allergies (usually a few hours after eating certain things) and can include bloating, wind, diarrhoea, itching, skin rashes and abdominal pain.

The most common cause of gut problems is irritable bowel syndrome (IBS), a catch-all term for a poorly understood constellation of symptoms including bloating, diarrhoea and constipation. It affects between 5 and 15 per cent of the population in Western countries.

IBS symptoms overlap with those of coeliac disease – an autoimmune disorder triggered by a protein called gluten, found in grains such as wheat, barley and rye. For coeliacs, consuming gluten causes symptoms such as diarrhoea, constipation, cramps and fatigue, and triggers a faulty immune reaction that damages the lining of the gut.

Although unrelated to IBS in origin, coeliac disease has been attracting attention because it is proving to be more common than previously thought, affecting 1 per cent of people. However, many who test negative for it – showing no signs of making antibodies in response to gluten, or of gut damage – still complain that wheat products make them feel unwell. This has been labelled non-coeliac gluten sensitivity, although the condition remains controversial.

Some argue that gluten is poorly digested by many people, and that its ubiquity in modern, processed food is at odds with the diet that the human gut evolved to

> “We are now understanding why so many people think they are sensitive to gluten”

deal with. Scepticism over whether gluten can cause symptoms in non-coeliacs has been fuelled by the fact that cutting it out has become a fashionable lifestyle choice.

Global sales of gluten-free food rose 12.6 per cent in 2016, and specialist supermarket aisles now heave with gluten-free products. In the US, the proportion of people eating a gluten-free diet more than tripled from 0.52 per cent in 2009 to 1.69 per cent in 2013, although the proportion who had coeliac disease stayed roughly constant.

Studies suggest that many non-coeliacs are choosing to avoid gluten because they believe doing so is healthy, despite little evidence for its benefits. Yet even if gluten is not itself the culprit, we are now understanding why so many people believe they are sensitive to it.

A growing body of evidence over the past few years points the finger at FODMAPs (short for fermentable oligosaccharides, disaccharides, monosaccharides and polyols). These carbohydrates are present in numerous foods, including wheat, which contains some called fructans. Switching to a gluten-free diet is likely to roughly halve your FODMAP consumption. Rather than having some sort of sensitivity to gluten, it seems that for some people with IBS, FODMAPs could be the trigger.

That was illustrated by a recent trial in which 59 non-coeliac adults on gluten-free diets were fed identical-tasting cereal bars packed with either gluten, fructans or neither. Those who had the fructan bar reported 15 per cent more bloating and 13 per cent more overall gut symptoms compared with the control group, whereas those who had the gluten bar felt no worse afterwards. “If gluten is a cause of IBS, it’s nowhere near as frequent as people say,” says Peter Gibson at Monash University in Melbourne, a pioneer of research in this area. Rather, fructans appeared to be the problem.

As well as being present in wheat and grains, fructans and other FODMAPs are found in fruits and vegetables such as onions, garlic, apples and chickpeas. MRI studies show that when digested, these compounds increase the production of gas and the volume of water in the bowel, causing distension. That doesn’t cause an issue for most people, but for up to 70 per cent of people with IBS, reducing intake of these foods provides relief from pain and bloating. The low-FODMAP diet is considered so effective for IBS that it is now recommended by the National Health Service in the UK and bodies including the Gastroenterological Society of Australia.

The type and quantity of FODMAPs that trigger symptoms varies enormously between individuals, but the worst offenders are those in onions, garlic, wheat, rye and barley. This variability means anyone embarking on a low-FODMAP diet should seek the help of a trained professional rather than relying on internet articles – although health authorities are still struggling to train enough people to meet the demand.

As the buzz around the low-FODMAP diet spreads, it is attracting attention for its potential in other gastrointestinal conditions, including acid reflux and indigestion. The diet is now being recommended in the management of inflammatory bowel diseases (IBDs) such as Crohn’s – conditions that are becoming more frequent in the West, possibly because of smoking and additives in the food we eat – and which are also associated with IBS-like symptoms.

Even so, eating a low-FODMAP diet isn’t the healthiest choice, if you can avoid it. One drawback

VITALINA/ISTOCK PHOTO

is that it cuts out foods that are important sources of vitamins, fibre and nutrients such as calcium. Recently, there have also been concerns that it depresses levels of good bacteria in the gut, and the long-term consequences of the diet remain unclear.

Many people trying to avoid FODMAPs struggle to work out which foods to eliminate. For one patient, it may be lettuce, for another tomatoes, and so on. Intriguingly, a third of people with IBS who try the diet reap no benefits at all. For them, some researchers are now looking at a more controversial alternative.

When it comes to gut health, one of the most common pieces of advice has been to eat plenty of fibre, such as wholegrain bread and fibrous vegetables, which help keep the gut working properly and can also reduce the risk of cancer and cardiovascular disease. But it now seems that fibre may also be part of the problem. Some types of fibre release gas when fermented in the bowel, causing irritation in sensitive individuals.

Peter Whorwell, a gastroenterologist at the University of Manchester, UK, was one of the first to demonstrate that reducing fibre could be beneficial in IBS, with a study finding that wheat bran made 55 per cent of people with IBS feel worse and only 10 per cent feel better. The idea has been gaining ground, although it has lately been overshadowed by the fuss over FODMAPs. Whorwell often advises his patients to try switching from wholegrain to white bread.

Whorwell even speculates that a push for healthier diets – high in fibre and fruit and vegetables – may be contributing to a rise in gut complaints. “Thirty years ago, nobody had heard of five a day,” he says. “It amazes me how many vegetables people are eating these days.”

Advising patients to eliminate both FODMAPs and fibre flies in the face of good nutrition. So, in future, IBS treatment will probably involve supplements containing targeted combinations of beneficial, slow-fermented fibres.

The good news for those with gut problems is that the diversity of symptoms and causes are being investigated like never before. For those who don’t, however, it might be time to step off the bandwagon: if you don’t have any symptoms, you don’t need to be on any of these diets. ■

THE MYSTERY OF ITCH

Got an itch? Then scratch it. We all have it from time to time, but it can be a serious problem if it doesn’t go away, and that’s left scientists scratching their heads – until relatively recently.

MEDIAPHOTOS/ISTOCK PHOTO

CHRONIC itch is a surprisingly common problem. It can come as a side-effect of opioid painkillers, the use of which has rocketed in recent years. It is associated with skin conditions such as eczema as well as nerve damage, kidney disease and allergies. An estimated one in five of us will experience chronic itch, defined as itchiness lasting for six weeks or more, at some point, and current remedies are providing little relief.

The most common treatments are antihistamines, which block the part of the immune reaction that causes itching when we are bitten by a bug, for example. Not all itches are immune-related, however, and antihistamines have proven to be ineffective for most forms of chronic itch. Neuropathic itch, which stems from damage to sensory nerves in the skin, has no effective treatment.

In recent years, researchers have discovered new kinds of receptor in the skin and spinal cord that play a role in the sensation of itch, and are working to figure out what naturally activates these receptors in the hope of designing drugs that can deactivate them.

For now, though, the single most effective way to get rid of an itch is what we do instinctively: scratch. But why do we rake our nails across our skin, when it causes pain and, potentially, tissue damage?

The answer lies in the way that the spinal cord is wired. Neurons that transmit long-distance messages between the body and the brain are bridged by smaller cells called interneurons. These can either be excitatory, spurring messages towards the brain, or inhibitory, stopping the messages dead. Scratching works because the body processes this sensation as more urgent than itch, so inhibitory interneurons halt the itch message and fast-track the pain signal instead.

Not all interneurons require pain to stifle itch though. For example, neurons that detect the sensation of coolness from a cold compress or menthol appear to make direct connections with a type of interneuron that prioritises the sensation of coldness over itch.

Researchers also recently identified another group of interneurons in the spinal cord that respond to a tickling sensation on the skin. Sensory neurons that transmit this kind of itch may be among the most sensitive neurons in the peripheral nervous system – but when stronger pressure activates other mechanically sensitive neurons, the tickle is stopped in its tracks to allow the stronger sensation to pass. The fact that pressure has the same effect on the interneurons as the pain caused by scratching suggests that rubbing can be as effective as scratching, and there is no need to tear at your skin with your nails.

The act of scratching also activates the brain's pleasure centres, which could explain why scratching an itch feels so good. This pleasure seems to be particularly strong for people with chronic itch conditions. Such individuals also appear to be more susceptible to contagious itch – that irresistible urge to join in when someone else is scratching. Contagious itch is thought to have evolved as a social signal, much like contagious yawning. The idea is that joining in when seeing someone else scratch would give people a head-start in dislodging any parasites that might be around. ▮

CHAPTER 3

PHYSICAL HEALTH AND AGEING

Advances in modern medicine during the past century have led to a remarkable improvement in life expectancy, largely thanks to our successful conquering of many infectious diseases. Yet as increasing numbers of us survive well into old age, chronic, non-communicable diseases like heart disease, type 2 diabetes and dementia are becoming more commonplace.

Although ageing is a risk factor for these conditions, they are not inevitable. Neither do we, biologically, age at the same rate. But the more we learn about these seemingly very different age-related diseases, the more similar their underpinning causes seem to be. Intriguingly, so too are the measures we can take to reduce our risks.

HOW OLD ARE YOU REALLY?

Age is a peculiar concept. We tend to think of it as the number of birthdays we have celebrated – our chronological age. But this is just one indicator of the passage of time. We also have a biological age, a measure of how quickly the cells in our body are deteriorating compared with those of an average person. Researchers are now starting to pin down what it means for our health when these two figures don't match up.

AGEING results from a progressive accumulation of cellular damage over time, resulting in a deterioration in our fertility, physical and mental capacity, an increased risk of disease, and ultimately, death. Yet these changes are only loosely associated with someone's chronological age.

The most widely cited theory of ageing is that telomeres, genetic caps on the ends of chromosomes, grow shorter each time a cell divides, like a wick burning on a candle. Once these are used up, the cell withers and dies. But a new idea gaining ground suggests ageing is instead a byproduct of how energy intensive it is for our bodies to continuously repair faults that occur in our DNA as cells divide. From an evolutionary perspective, there is little reason to maintain that process for ever, after an age when we would normally have reproduced. Little by little, faults build up in cells and tissues, causing us to deteriorate.

This is where biological age comes in. It attempts to identify how far along in this process we have come. This is no simple task, given the many different biological processes at work, but a growing number of researchers have taken up the challenge.

DANIEL STOLLE

For instance, Daniel Belsky and his team at Duke University in North Carolina have studied ›

18 different markers of cellular ageing, including blood pressure and cardiovascular function, in almost 1000 adults. This revealed that some individuals were ageing far faster or slower than their birth certificates suggested. One 38-year-old had a biological age of 28; another's biological age was 61. Such biologically old young people fared worse on physical and mental tests compared to those whose biological and chronological ages were more similar.

Of course, we all know people who look young for their age, or folks who seem prematurely wizened. At least some of these age-related molecular changes are reflected in your face. In 2015, Jing-Dong Jackie Han and colleagues at the Chinese Academy of Sciences in Shanghai analysed 3D images of more than 300 faces of people between 17 and 77 years old, and created an age-prediction algorithm. Using it on a new group of faces, they found that people born during the same year differ by six years in facial age on average, and that these differences increase after 40. High levels of low-density "bad" cholesterol come with puffier cheeks and pouches under the eyes, for instance. Dark circles under the eyes can result from poor kidney function or blood circulation. The message is that if we look older than we should, it could be a sign of underlying ill health.

Other changes are reflected in the blood. Insilico Medicine in Rockville, Maryland, has developed a deep-learning algorithm to predict people's biological age, based on 32 different blood parameters which are often assessed during a routine clinical blood test. People whose blood age is higher than their actual number of years are more likely to have health problems, they have discovered. The algorithm is free to use; you simply plug in your parameters at www.aging.ai.

James Cole and colleagues at Imperial College London have even found a way to estimate the age of people's brains, based on a brain scan. They found that people whose brain age was older than their chronological age had poorer lung function, slower walking speed and an increased risk of death. Those with older brains also performed worse on tests of logic and pattern recognition.

What makes the brain age prematurely? High blood pressure, smoking and high cholesterol seem to accelerate brain ageing, possibly by affecting the blood vessels that carry oxygen and essential nutrients. Long-term stress has also been shown to speed up memory loss in older adults. And shift work has a big impact: more than 10 years of shift work can accelerate brain age by around 6.5 years. Exercise seems to be key to mitigating these harms. The brains of elderly people who regularly exercise look 10 years younger than those who don't.

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There's more on exercise later in this chapter

Yet, even in the same individual, different parts of the body can age at different speeds. Epigenetics refers to the process by which chemical tags called methyl groups are added to or removed from DNA. This in turn influences which genes are switched on or off. Some of these changes in methylation patterns over time can be used to estimate age. The father of this technique is Steve Horvath at the University of California, Los Angeles. In 2011, looking at methylation patterns in

“Research shows that some parts of the body age more quickly than others”

blood samples, Horvath and his colleagues were able to predict chronological age to within five years. He has since analysed data from more than 13,000 samples and identified methylation patterns to estimate a healthy person’s age to within 2.9 years.

The results show that some parts of the body age quicker than others. A recent analysis of breast tissue from healthy women in their twenties revealed it was epigenetically roughly 17 years older than their blood, which tends to correlate closely with chronological age. Horvath thinks that breast tissue ages quicker because of constant exposure to hormones.

This difference decreases as we get older; for women aged 55 years, breast tissue was around eight years older than blood. By identifying what these normal differences look like, we might identify women whose breast tissue is prematurely aged, requiring closer monitoring for cancer. Horvath has also shown that the heart tends to age more slowly, possibly because it is constantly regenerated by stem cells.

Beyond monitoring and aiding diagnoses for diseases, some of these measures could give us an indication of how much life we have left, although it is not very accurate, yet. Around 5 per cent of the people Horvath studied had an accelerated epigenetic age, and their risk of death in the next decade was about 50 per cent higher than those whose epigenetic age lined up with their actual years.

Is there anything we can do to intervene? Horvath has started studying the epigenetic age of induced pluripotent stem (iPS) cells, adult cells that can be pushed back into an embryonic-like state, from which they can re-differentiate into almost any cell type in the body. The epigenetic age of iPS cells is zero.

Transforming all our body cells back into stem cells would be extreme, but possibly this strategy could be modified to rejuvenate some of them. “All epigenetic marks are reversible, so in theory it’s possible to reset the clock,” Horvath says. Another promising, if speculative, plan might be to freeze blood stem cells when you are young so that you can use them to reconstitute your immune system when you are old.

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Chapter 6 has more on reversing ageing

Short of miraculous anti-ageing treatments, understanding more about biological age can still improve our health. People told their heart age – measured using parameters such as blood pressure and cholesterol – are better able to lower their risk of cardiovascular problems compared with people given standard information about heart health, for instance.

There are not yet any placebo-controlled trials to determine whether certain lifestyle interventions can reduce biological age, and so risk of early death. But Horvath did find that the epigenetic clock is accelerated in the livers of obese people, and ticks more slowly for those who regularly consume fish and vegetables, and only drink in moderation.

Again, exercise also seems to help. In a trial of more than 57,000 middle-aged people, those with more youthful fitness levels were less likely to die in the decade or so after. This fitness-associated biological age was a stronger predictor of survival than chronological age. Age really is just a number, it seems. ▮

AGEING AND INFLAMMATION

We saw in chapter 1 how our immune systems keep us safe from infectious agents, but also how one protective responses to infection and injury – inflammation – is at the root of many age-related diseases. A better understanding of this process could help buffer our bodies against the stresses modern life throws at them, and keep us healthier into old age.

INFLAMMATION is the body's first line of defence. Without it, we would be at the mercy of every pathogen going. When the body's protective barrier has been breached by injury or infection, the classic inflammatory response brings redness, heat, swelling and pain. The body's immune and repair processes kick into action, and over the course of several days or weeks, the problem is resolved.

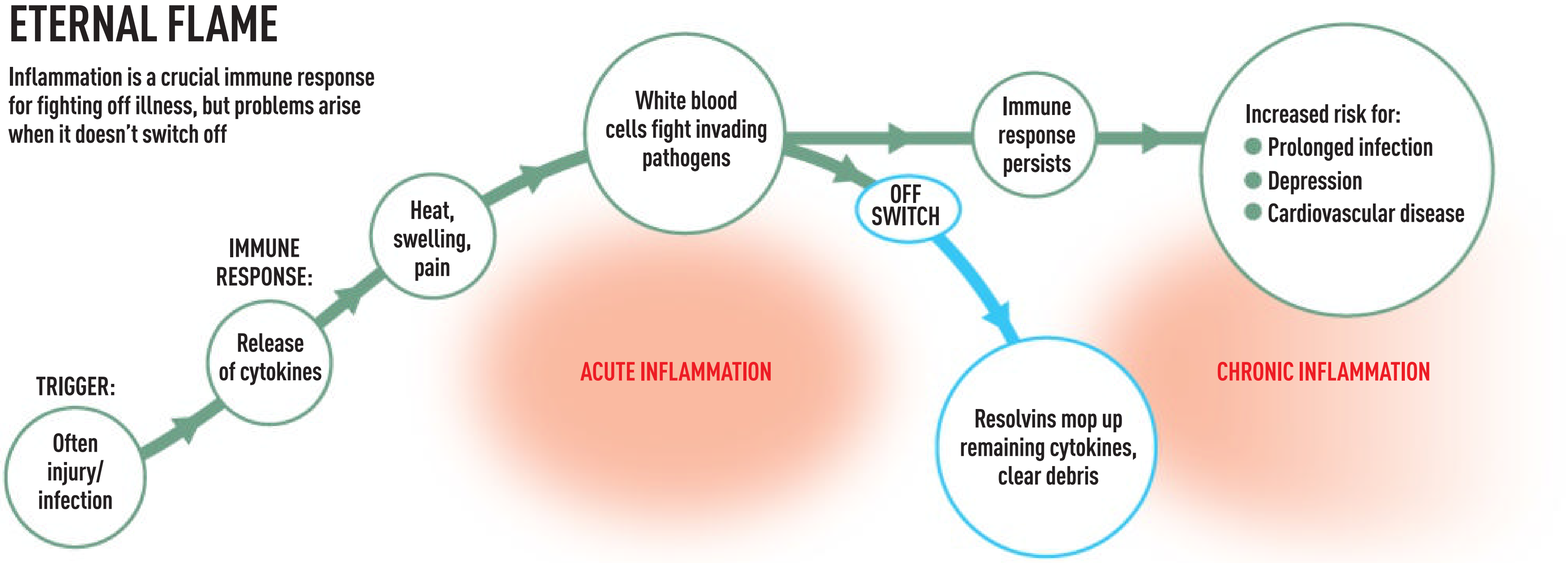
Except sometimes it's not. Throughout our evolutionary history, acute inflammation has mostly worked just fine, flaring up, tackling the problem and dying away again when the danger has passed. But now modern life is stacked against this delicate balance. Obesity, stress, pollution, bad diet and ageing can all tip us into a low-level state of inflammation that, rather than being confined to a specific tissue, keeps the entire body in a perpetual state of readiness for a threat that never comes.

This persistent background inflammation might not always make us feel ill, but it can store up problems for the future, from heart disease to type 2 diabetes and neurodegenerative disease. In 2008, immunobiologist Ruslan Medzhitov of Yale University dubbed this "para-inflammation", and argued that it is an unfortunate consequence of our longer, calorie-rich lives.

Stress is a particular problem. The hormone noradrenaline, which is released in anticipation of an impending life-or-death situation, sets off the same chain of events as an infection or injury. Yet although stresses passed quickly in our evolutionary past, these days many of us are walking around with a ticking time bomb of stress-induced inflammation that never quite goes away. Even everyday stresses can be a problem. For example, Nicolas Rohleder of Brandeis University in Massachusetts has demonstrated that the long-term

ETERNAL FLAME

Inflammation is a crucial immune response for fighting off illness, but problems arise when it doesn't switch off



strains of caring for a seriously ill family member, and a series of short-term stresses, both increase levels of inflammatory markers in otherwise healthy people.

Obesity is another inflammation-inducing modern disease. A small amount of body fat is healthy, and in fact necessary for regulating not just the immune system, but also appetite, mood and metabolism. Once the scales tip past 25 to 30 per cent body fat, however, the balance shifts. Body fat stores large quantities of inflammatory cytokines, and if there is too much fat on board, particularly around the organs, they can seep out, leading to ongoing, low-level inflammation.

Modern, high-sugar diets can also lead to gum disease, which pushes the body into an inflammatory state that has been linked to an increased risk of atherosclerosis: fatty deposits in the arteries that are one of the main risk factors for heart attacks and strokes.

The longer these inflammatory markers hang around, the more likely they are to cause problems. These can be relatively minor, prolonging colds by keeping up the response when it is no longer needed, for instance. Or they can be life-threatening. A recent study of nearly 300 people found that inflammation is directly linked to the early stages of heart disease. Over the course of three years, people with higher levels of reported stress and stress-related brain activity not only had higher levels of C-reactive protein, a marker of inflammation, but also had a greater risk of cardiovascular disease. It seems that when there are higher levels of white blood cells in circulation, they get attracted to any fatty plaques accumulating in the arteries, making these more likely to build up and eventually rupture. This can lead the vessel wall to bleed and form a clot, which could go on to cause a heart attack or stroke.

Chronic inflammation might also increase the risk of depression. Many of the psychological symptoms that come with such inflammation – tiredness, malaise and a loss of appetite – look a lot like depression. Some people are beginning to wonder if a rumbling level of inflammation is behind at least some cases of depression and other mental health problems. This might be the reason why antidepressant drugs, which don't reduce inflammation, are often ineffective.

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See Chapter 4 or more on mental health issues

The key then seems to be to keep the life-saving properties of the acute inflammatory response without allowing it to become chronic. But how?

One clue came in 2000 when Charles Serhan at Harvard Medical School and his team revealed that inflammation has an off switch. Until then, the reaction was thought to peter out as the immune cells that secrete cytokines gradually reduced in number and their effects became diluted. In fact, Serhan found that neutrophils and macrophages, the types of white blood cell that kick off the process, actively change tack once it has got going, releasing a second set of chemicals, called resolvins, that help mop up any remaining cytokines and sweep away any debris.

This made Serhan and others wonder whether chronic inflammation might be caused not by the on signals being turned up too high, but by a problem with the off switch. In the years since, he has been studying resolvins and related chemicals to see if there is a way to harness or mimic their actions.

One fly in the ointment is that there is so far no way to tell the difference between the various stages of acute inflammation – from a cut or cold, perhaps – and more troublesome chronic, low-level inflammation. ›

That's partly because immune cells and cytokines circulate around the body all the time, so any snapshot of the blood or tissues might make them seem inflamed when actually they are healthy.

Serhan thinks that looking at levels of circulating resolvins might be a better option. He has found that people with type-2 diabetes tend to have higher levels of cytokines in circulation, but lower levels of resolvins. This is relevant because the same white blood cells that kick-start the inflammation response should also step in to secrete resolvins to end it. So, if someone has lots of cytokines but few resolvins, it is a sign of chronic inflammation – and a problem with the off switch.

Serhan has also been working with periodontal researcher Thomas Van Dyke of the Forsyth Institute in Cambridge, Massachusetts, on a mouthwash containing resolvins. In rabbits, the mouthwash not only cleared up their inflamed gums, it also reduced inflammatory markers for cardiovascular disease. Human trials are now under way.

As well as finding ways to diagnose and treat low-level inflammation in healthy looking people, researchers are searching for drugs to stimulate the body to resolve inflammation in those with chronic conditions such as arthritis and inflammatory bowel disease. The current generation of anti-inflammatory drugs, including steroids and non-steroidal anti-inflammatories such as ibuprofen and naproxen, inhibit the onset of inflammation, but do nothing to bring it to an end. Taking these drugs can reduce painful swelling in the joints, but by turning down the immune response, they leave people more vulnerable to recurring infections and less able to fight off a virus or recover from an injury.

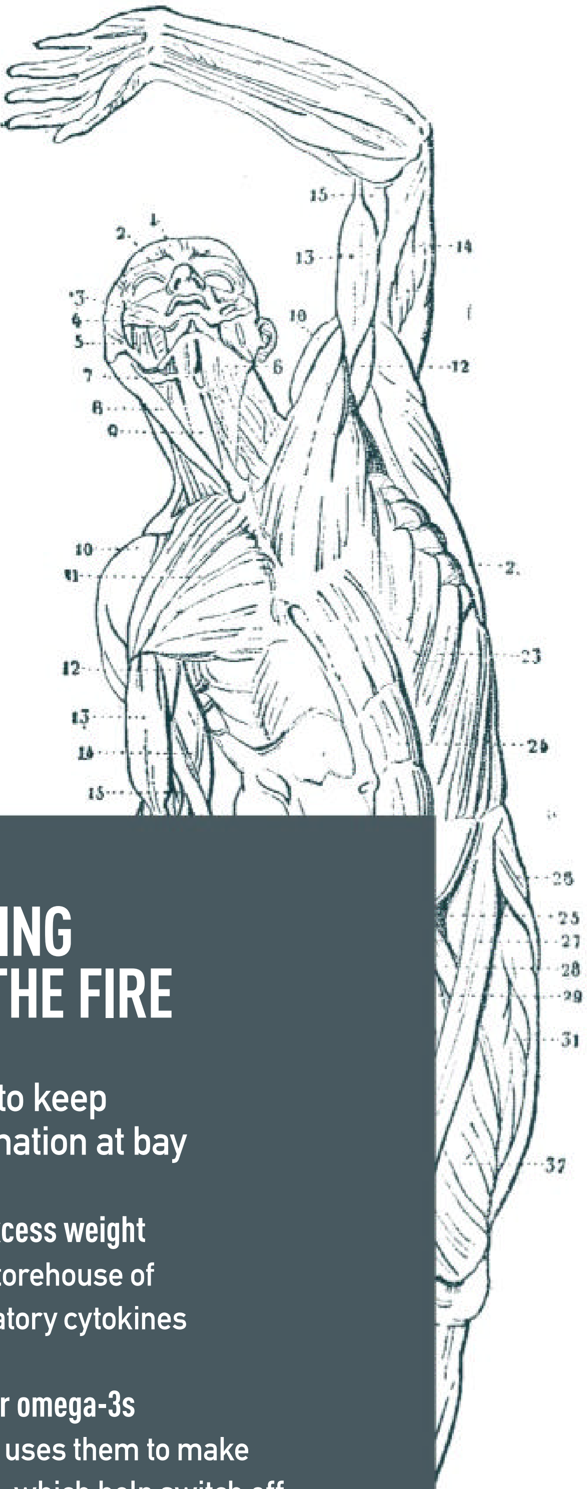
Resolvins, on the other hand, actively tackle one of the root causes of inflammation by helping to rid the body of foreign bacteria and viruses. Boosting their levels may therefore help solve the problem, rather than just masking its effects. Trials of new treatments are under way, but the only drug now available that has some resolvin-like effects is aspirin. It does block pro-inflammatory mediators, but Serhan's group has found that low-dose aspirin has another unique ability: to trigger the production of more stable versions of natural resolvins. With currently available drugs, there is only one thing you can do to jump-start resolution of inflammation. "Take low-dose aspirin," Serhan says.

That may soon change, however. Researchers led by Derek Gilroy at University College London are trialling a new drug called anabasum that mimics natural painkillers called cannabinoids in the body. So far, it is proving to work as well as steroids at preventing inflammation, but with fewer side effects. It also actively clears bacteria from wounds. Experiments so far have focused on skin inflammation, but the drug has since been tested in cystic fibrosis with promising effects.

Pain-relieving drugs could also benefit from a new understanding of how inflammation comes to an end. Resolvins have been found to regulate pain, and their receptors have been identified in the dorsal root ganglion, a kind of junction between the sensory nerves and the spinal cord. Assuming they can be harnessed therapeutically, they could someday even replace opioids, providing a pain control mechanism that wouldn't lead to addiction.

Exciting as they are, resolvins are unlikely to provide a complete solution. The reason inflammation seems to be at the root of so many health problems is probably because it is not one thing, but many. This was demonstrated in recent experiments where Gilroy's team injected bacteria under the skin of people with rheumatoid arthritis – a painful condition characterised by chronic inflammation often due to autoimmune disease. Their arthritis-related inflammation remained, but they had no problems in shutting down the skin-based inflammation that followed the injection. The two types of inflammation, and their resolution pathways, seemed to be completely different. This is also true for the same disease in different people, as well as for different tissues in the same person. Then there are gender differences in susceptibility: for some unexplained reason, women are far more likely than men to get autoimmune diseases.

Pinning down the solutions – and even figuring out which to use in which instance – won't be simple. "It's like you walk into a bar and there is a great big bar-room



PUTTING OUT THE FIRE

5 ways to keep inflammation at bay

1. Lose excess weight
Fat is a storehouse of inflammatory cytokines

2. Eat your omega-3s
The body uses them to make resolvins, which help switch off inflammation

3. Exercise
Being active releases anti-inflammatory chemicals and tells the liver to metabolise fat

4. Stretch
Extending inflamed muscles seems to soothe them in rats

5. Take low-dose aspirin
The only currently available drug that stimulates cessation of inflammation (check with your doctor first)

brawl, but you don't know who is involved, and you don't know who started it and how it's going to end up," says Gilroy. "Teasing and separating these separate factions will make it much easier to understand the processes going on."

While we wait for these insights, there are simple things we can do at home to keep inflammation at bay (see "Putting out the fire", left). All the resolvins identified so far are manufactured in the body from omega-3 fatty acids, which we get from our diet, the richest source being oily fish. So, ensuring we get the recommended three weekly portions of oily fish, or equivalent, might help ensure that our bodies have enough raw material to wind down inflammation. This may explain why a diet rich in these fats is associated with a lowered risk of heart disease.

Certain kinds of exercise seem to help, too. In recent experiments in rats with inflammation of the back, yoga-like stretching of the affected muscles twice a day stimulated the release of resolvins within the muscle, which enabled the rats to regain full movement and heal more quickly than control rats. Researchers are currently investigating whether this "yoga experiment" also works in human volunteers.

Studies are also linking fat- and sugar-rich diets to greater levels of inflammation. This, combined with research suggesting that pigments found in fresh fruit and vegetables help to regulate inflammation, indicate that the standard advice about eating well applies here too: consume fewer processed foods and plenty of whole grains, fruit and vegetables.

What about celebrity endorsements of basil-leaf infused bubble baths or turmeric lattes to curb inflammation? The jury is out. Curcumin, the active ingredient in turmeric, has anti-inflammatory properties in cells in a Petri dish, but clinical trials in humans have so far been underwhelming; most of it passes through the body without being absorbed. Likewise, quite how the basil in your bath is supposed to infuse into your body is anyone's guess. But if it helps you unwind – and provided following the latest fads don't create their own stresses – go for it. In the fight against chronic inflammation, every firefighter helps. ∎

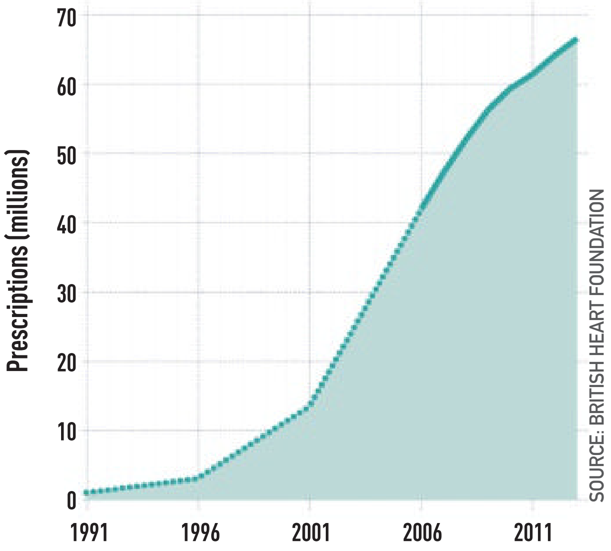
STATINS AND HEART HEALTH

Any discussion of maintaining a good level of physical health into old age can't get around talking about the heart, the organ that untiringly pumps blood around our body, supplying its cells with oxygen and essential nutrients.

Untiringly, that is, until it tires. Heart disease and strokes, in which the blood supply to parts of the brain gets cut off, are now the world's biggest killers. Statins, drugs that lower cholesterol, which in turn lowers heart-disease risk, are seen by many as the answer. This official line justifies many people popping these pills – but the evidence is not so clear-cut.

STATINS ON THE UP

The number of cholesterol-lowering drugs prescribed in England ballooned with the advent of statins – a pattern repeated across the developing world



SOURCE: BRITISH HEART FOUNDATION

IN WEALTHIER parts of the world, heart disease and strokes now account for over a quarter of deaths. Many factors are at play, with conventional wisdom identifying cholesterol as one of the biggest culprits. A fatty biomolecule synthesised primarily in the liver, cholesterol forms cell walls and the myelin sheaths that protect neurons in the brain. It plays a part in biological processes from cell signalling to making vitamin D, and may even help fight infections.

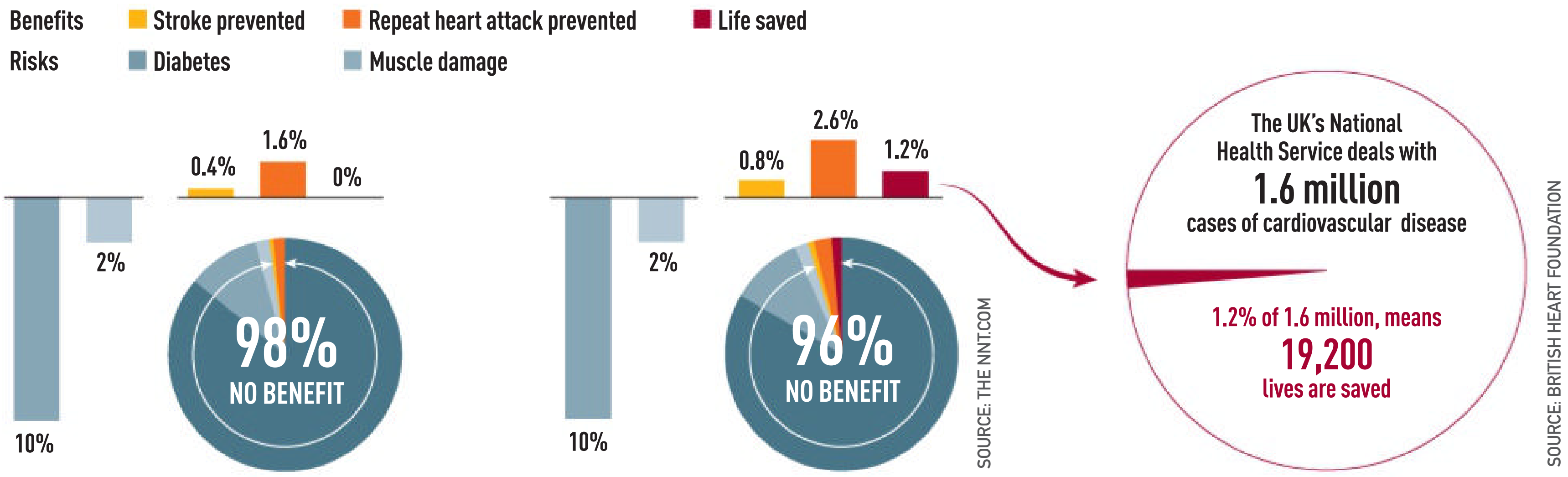
But a dark side has long been suspected. In 1913, Russian pathologist Nikolai Anichkov showed that rabbits fed pure cholesterol extracted from egg yolks developed higher cholesterol levels in their blood. Since then we've learned how excess cholesterol, carried in the bloodstream by lipoproteins, can stick to artery walls, restricting blood flow and making clots more likely – the condition known as atherosclerosis.

The connection between cholesterol and heart disease became widely accepted in 1984, with the publication of the results of the Lipid Research Clinics Coronary Primary Prevention Trial. This followed about 3800 middle-aged men over seven years, showing that lower levels of "bad" low-density lipoprotein cholesterol correlated with a reduced risk of a heart attack, fatal or otherwise, or having to undergo heart bypass surgery.

Enter statins. These drugs work by inhibiting the production of an enzyme crucial for making cholesterol in the liver. In the UK, official guidance is that people with normal levels of cholesterol should take statins if their risk of a stroke or heart attack within

GOOD FOR THE HEART?

One measure of a treatment's effectiveness is how many people can expect a certain outcome, positive or negative, in a certain time



SOURCE: THE NNT.COM

SOURCE: BRITISH HEART FOUNDATION

Patients with no known heart disease treated with statins for five years

Patients with known heart disease treated with statins for five years

That's potentially still a lot of lives saved

10 years is deemed to be higher than 10 per cent. The American Heart Association's recommended trigger level is 7.5 per cent.

The first commercial statin received approval in the US in 1987, with plenty more marketed in the next decade. Many trials showed that they reduced heart attacks and strokes in people with high cholesterol or who were otherwise at high risk of heart disease – who smoke, don't exercise, are overweight and so on

More recently, studies have extended the benefits to people at lower risk. One key trial known as JUPITER, published in 2008, looked at the effects of taking rosuvastatin on 17,800 people with no known history of heart disease. These people had cholesterol levels below then-recommended thresholds for treatment with statins, but increased levels of a biomarker known to correlate with an increased risk of future heart problems. Over five years, incidence of heart attack among those who took statins more than halved.

Such results led the American Heart Association to update its advice on who should receive statins in 2013. The UK's National Institute for Health and Care Excellence (NICE) followed suit in 2014.

But right from the start, JUPITER and other similar studies have caused controversy. For a start, heart attacks may have halved in the JUPITER trial, but the absolute incidence of heart attacks in the study population was low anyway. Only 99 people had a fatal heart attack during the trial period, 31 of whom were taking the statin. Viewed that way, less than 0.5 per cent of the people treated with rosuvastatin benefited, casting a different light on the drug's effectiveness.

Similar caveats arise in other analyses. As highlighted in a 2014 editorial in the Annals of Internal Medicine, for example, two meta-analyses of studies from 2012 and 2013 managed to come to opposite conclusions about statins' effectiveness, despite the mortality levels they found differing by less than half a per cent.

An alternative measure of a drug's efficacy is "number needed to treat" (NNT), the number of people that have to be given a therapy for a specified time for one to benefit. Analysis undertaken by TheNNT.com, a website run by a consortium of physicians and medical researchers aiming to put a patient's perspective on research data, suggests that people with existing heart disease clearly benefit by taking statins: 1 in 83 people, or 1.2 per cent, have their life saved over five years. In the absence of diagnosed heart disease, however, no such clear-cut statement is possible. A separate meta-analysis in 2013 led by John Abramson at Harvard University, found that "140 low-risk people must be treated with statins for five years to prevent one major coronary event or stroke". Not only that, but there was no reduction in the overall mortality rate from all causes in that period.

Such figures mean there should be no blanket prescription of statins, Abramson reckons: "Why would you impose the decision on people when it is at best a judgement call?"

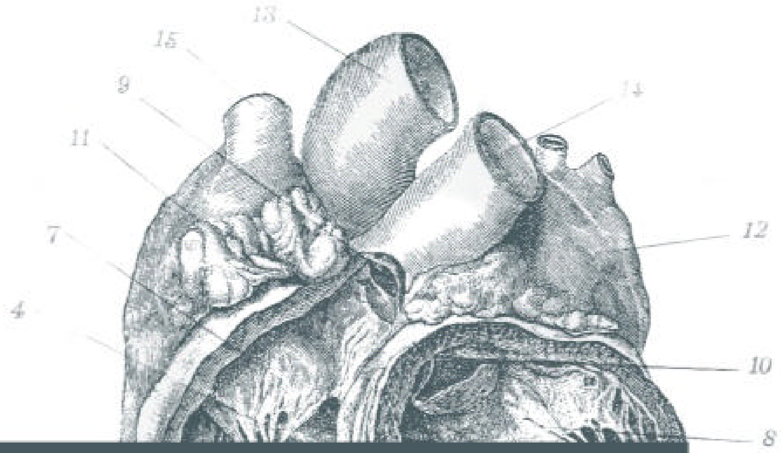
Others beg to differ. Rory Collins leads the Cholesterol Treatment Trialists' (CTT) Collaboration based in Oxford, UK, which has access to by far the largest database of statin trials. He points out that even these low NNT figures, extrapolated to whole populations, equate to hundreds of thousands of people avoiding heart attacks. That is worth it, even › without life extension. "If you've seen someone who's had a non-fatal heart attack or stroke, you'll know it completely changes their physical and psychological life," he argues.

Yet statins are not without side effects. Muscle pain, or myalgia, is the most commonly cited one, with some patients reporting feeling weak and achy whilst taking them. According to a review paper of clinical trials by Collins, Liam Smeeth at the London School of Hygiene and Tropical Medicine and others that was published in 2016, statin therapy causes muscle pain in about 50 to 100 patients, per 10,000 treated for 5 years – less than one per cent. But other studies have found far higher figures – a quarter or a third, and in one study based in Paris, 87 per cent of participants complained of pain. In 2016, David Spence and George Dresser at the University of Western Ontario in Canada wrote in the *Journal of the American Heart Association* that, despite claims from clinical trial data that adverse reactions are vanishingly rare, in the real-world, myalgia and cramps may be more are more common.

Humans are highly suggestible, meaning reports of muscle pain caused by statins may cause other people to feel it too. But some researchers contend that a flaw in the design of trials so far means those who experience side effects tend to withdraw before a trial's formal start.

Concerns have also been raised about a potential link to type 2 diabetes. Here, the evidence seems less solid: The US Food and Drug Administration advises that "a small increased risk of raised blood sugar levels and the development of Type 2 diabetes have been reported with the use of statins", but this may just be an artefact of the way we define diabetes: even if statins cause a small rise in blood sugar, this is unlikely to cause the kind of damage we associate with severe, long-standing diabetes.

So, what to do? In June 2016, NICE made it clear that patients taking statins are entering a health lottery. These drugs probably do save some lives – it is just impossible to predict which ones. And, of course, we'll never know, because those who benefit don't have a heart attack. Meanwhile, exercise, good diet and a stress-free lifestyle are proven heart medicines. ∎



WHAT MAKES A HEALTHY TICKER?

Many factors beyond blood cholesterol determine how healthy your heart is

BEING YOUNG.
Muscle tissue tends to degrade with age, making your heart work that little bit harder with every passing year.

BEING FEMALE.
Before age 60, men are at greater risk of heart disease than women. Overconsumption, smoking and work stress have all been blamed – but no one truly knows why.

GOOD GENETICS.
Some predisposition to heart disease is hereditary, although we haven't singled out what genes are responsible. Lifestyle factors such as smoking or poor diet passed between generations may also contribute to a "hereditary" element.

LOW BLOOD PRESSURE.
This reduces the risk of ruptured arteries, dislodged clots or plaque causing a stroke – stress, overeating, smoking and alcohol consumption all play a part in pushing it too high.

HEALTHY BODYWEIGHT.
The heart has to work harder in people who are obese. Keeping trim also reduces incidence of type 2 diabetes, another risk factor for heart disease.

REGULAR EXERCISE.
Like any other muscle, the heart grows stronger when forced to do a reasonable amount of work. Exercise also helps keep weight and blood pressure down.

WHY EXERCISE IS THE BEST MEDICINE

Everyone knows that booze, tobacco and unhealthy eating are bad for us. But if physical inactivity was packaged and sold as a product, it would need to carry a health warning. Besides its effects in warding off diabetes and obesity, and lowering the risk of heart disease and stroke, a plethora of recent studies shows that exercise protects us from cancer, Alzheimer's disease, depression and more. It even boosts memory. But how much exercise should we be doing, what sort, and how often?

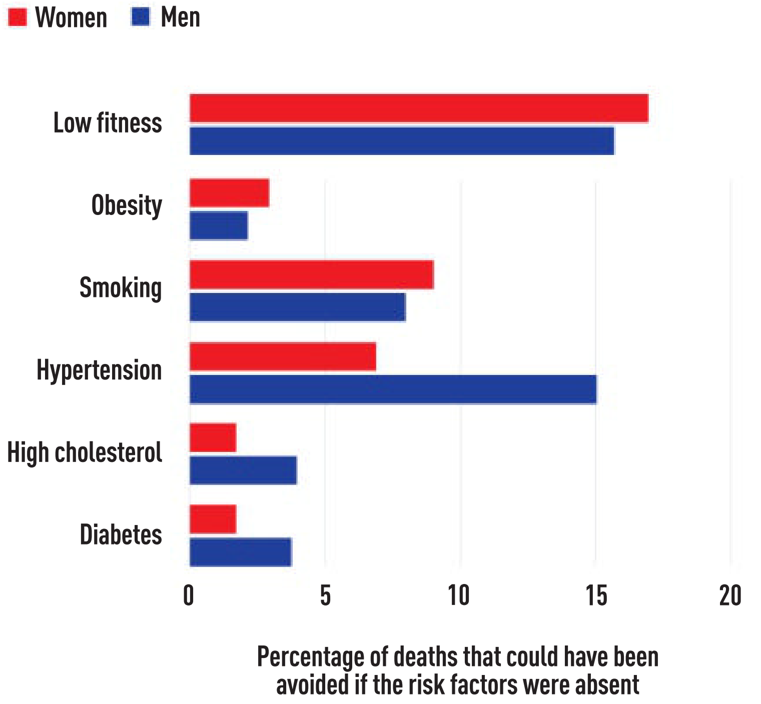
THROUGHOUT evolution, humans have been active. Our ancestors chased prey as hunter-gatherers and fled from predators. More recently, they laboured on farms and in factories. But the decline of agricultural and industrial labour, plus the invention of the car, a multitude of labour-saving devices and – most perniciously – TV, computers and video games, mean we've all ground to a sudden and catastrophic standstill.

Now we are paying the price. In 2009 Steven Blair, an exercise researcher at the University of South Carolina in Columbia, published a study of more than 50,000 men and women showing that a lack of cardiorespiratory fitness was the most important risk factor for early death. It accounted for about 16 per cent of all deaths in men and women over the period of study, more than the combined contributions of obesity, diabetes and high cholesterol, and double the contribution of smoking.

But if physical inactivity is killing us, the good news is that we can do something about it. Even a small amount of exercise brings significant health gains. This was the case in a huge study from 2011 that followed more than 400,000 people in Taiwan over an average of eight years, noting their exercise habits and the number of deaths from different causes. This showed that just 15 minutes a day of moderate exercise such as fast walking was enough to reduce risk of death by 10 per cent compared with sedentary participants. This effect could also be gained by around 5 minutes of vigorous exercise such as running. ›

EXERCISE OR DIE

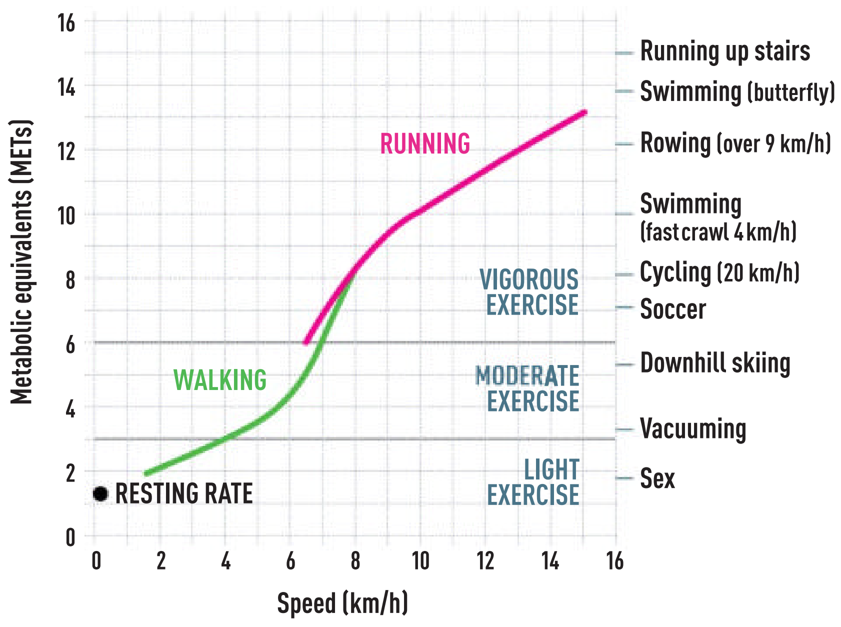
Based on a study of 54,000 people in the US



SOURCE: BRITISH JOURNAL OF SPORTS MEDICINE, VOL 43, P1

MEASURING THE BURN

The energy expended during exercise can be measured in metabolic equivalents (METs), where 1 MET is the metabolic rate at rest. Walking counts as vigorous exercise, if you go fast enough



SOURCE: COMPENDIUM OF PHYSICAL ACTIVITIES

But it is not all about aerobic exercise. Since 2011, UK exercise guidelines have stated that all adults should perform muscle strengthening activities two days a week, in addition to the recommended 150 minutes of aerobic activities a week – running, brisk walking, swimming or anything that gets your heart pumping and you breathing faster.

At least some benefits of strong muscles have been appreciated for centuries (even Socrates told his disciples that it was a disgrace to grow old without developing their physical strength to the highest limit), but it is only recently that we have come to appreciate just what our muscles can do for our health.

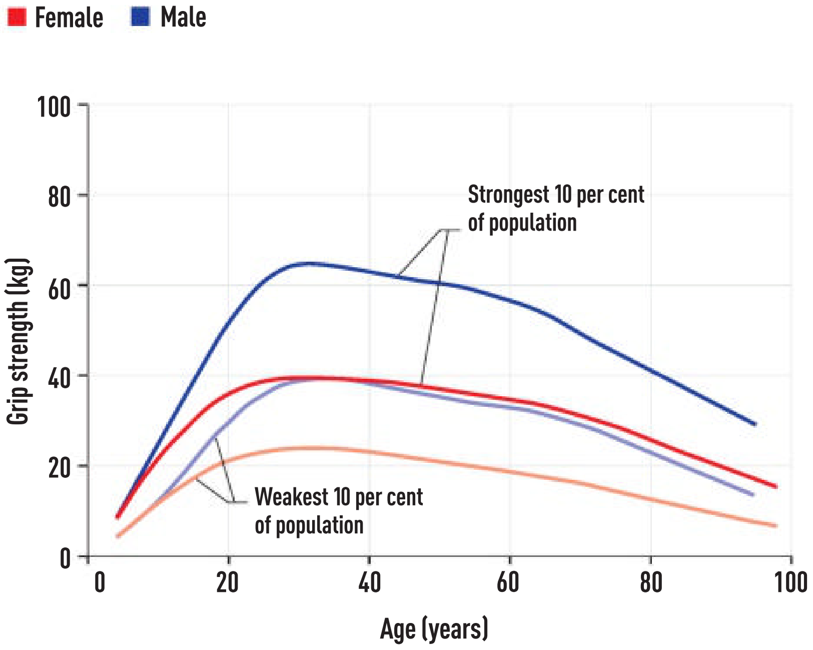
Age-related muscle loss happens to everyone. Around the age of 30, we start to lose up to 5 per cent of our muscle mass each decade, and this accelerates at 70. Muscle composition also changes, with “type two” fibres, which help us bear heavy loads for short spells, being replaced by “type one” fibres that are more efficient over long periods but less able to carry weight. Our muscles also stop using protein as efficiently and so are less able to repair themselves. These age-related changes have many causes, including alteration in the levels of hormones such as testosterone, and a reorganisation of brain cells that control movement.

In the past, efforts to tackle muscle loss were focused on people in their later years, but now a mountain of evidence points to the benefits of fighting muscle wastage throughout life.

> “A mountain of evidence points to the benefits of fighting muscle wastage”

STRENGTH VS AGE

Overall muscle strength can be assessed by measuring grip strength. This peaks in early adulthood and then declines, with big differences between men and women and between the strongest individuals and the weakest



SOURCE: DOI.ORG/GBSFZS

The best evidence comes from studies of the exercise habits of large numbers of people. One showed that lifting weights for less than an hour a week reduces the risk of heart attack and stroke by up to 70 per cent, independent of any aerobic training. Another study of 100,000 women found that those who did at least an hour a week of strength training significantly lowered their risk of type 2 diabetes. And people with better grip strength – a proxy for overall muscle strength – have a lower risk of cardiovascular disease and cancer and are at reduced risk of premature death by any cause.

One reason stronger muscles keep us healthier is that they help prevent the debilitating effects of wobbles, falls and problems moving, increasing well-being in the process. For instance, when residents at a nursing home performed one set of six resistance machine exercises twice a week for 14 weeks, they not only increased their overall strength by 60 per cent, but also improved their ability to live independently by having the power to cope with everyday activities like getting to the bathroom.

Muscle also plays an important role in regulating the body's glucose levels. With the help of insulin, it soaks up glucose from the blood and stores it in the form of glycogen. Bigger muscles mean a bigger sink for glucose and a higher number of cells that transport and clear glucose from the body, which all helps ward off type 2 diabetes, in which blood glucose levels become too high.

And while you don't have to look like a bodybuilder to reap the benefits, having bigger muscles is also linked with better survival rates for people with cancer, probably because the disease decreases muscle mass, so it is helpful to have a bigger resource to start with to keep the body going for longer.

Another surprising benefit of strength training is how it burns calories, even after the exercise is over. Weight training increases your basal metabolic rate – the amount of energy your body consumes when at rest – in two ways.

First, bigger muscles require more energy to fuel their tissue maintenance. So simply having more muscle mass uses more calories. Second, in the short term, lifting weights causes tiny tears in your tissue that require a relatively large amount of energy to remodel. This increase in energy demand can last three days after a workout.

Let's say you fit in two 20-minute resistance training workouts a week. Each online session requires about 200 extra calories to perform, but over the next three days, you will use another 100 extra calories a day to help repair your muscles. Over the month, those two workouts a week have consumed a whopping 5000 extra calories – without even leaving the house.

All of this helps if you want to decrease body fat, a factor associated with lower cholesterol, lower blood pressure and improved insulin sensitivity and glucose control, all of which contribute to a decreased risk ›

The "Mediterranean" diet has been credited with being most healthy

WUNDERVISUALS/ISTOCK PHOTO

WHAT'S THE HEALTHIEST DIET?

So what do we know about what actually constitutes a healthy diet? If you had asked this question ten years ago, the answer would have come back loud and clear: plenty of fresh fruit and vegetables, grains and nuts, a bit of fish and poultry, olive oil instead of butter, a glass of wine with your food – but go easy on the red meat, dairy and refined sugar.

Often called the "Mediterranean diet", it originates in the work of US researcher Ancel Keys. Starting in the 1950s, his pioneering Seven Countries Study established that countries around the Mediterranean Sea thought broadly to follow this sort of diet had lower levels of heart disease and greater longevity. After poring over his huge data set, Keys concluded that there was a clear association between saturated fat intake and incidence of cardiovascular disease.

This became known as the lipid hypothesis, which has been called "possibly the most influential idea in the history of human nutrition". The Mediterranean diet has been widely lauded as the recipe for a long and healthy life. Dietary guidelines in the UK, the US and elsewhere reflect its key messages, especially on meat and dairy.

More recently, however, well-publicised doubts about Keys's methods and conclusions have begun to circulate. One common complaint is that he cherry-picked data to support his pre-existing views about fat, ignoring countries such as France that had high-fat diets but low rates of heart disease. The strongest evidence in favour of a low-fat diet came from Crete, but it transpired that Keys had recorded some food intake data there during Lent, a time when Cretans traditionally avoid meat and cheese, so their diets appeared to be less fatty than they actually were.

Nutrition research is, by its very nature, difficult and imprecise, and one-size-fits-all solutions hard to come by. But those hoping that fat and sugar and red meat are back on a healthy plate are probably in for a disappointment. In recent years, the pendulum has begun to swing back. The fine details probably need a rethink, but in broad-brush terms a "Mediterranean" style still holds up. A lot of research supports the idea that the healthiest diets we know of feature primarily unprocessed foods, with lots of fruit and vegetables, and limited meat and saturated fat.

But more important even than what you eat is how much. Moderation is key, with a body of research growing that even intermittent fasting can increase longevity. In fact, sensible dietary advice can probably be summed up simply in seven words first coined by the US author and activist Michael Pollan: "Eat food. Not too much. Mainly plants."

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of type 2 diabetes and cardiovascular disease. This is one of the reasons why getting stronger protects you from heart attacks.

But strength training really trumps aerobic exercise with its effect on bone. Our bones start to degrade as we age, losing mass and making us more prone to fractures. Aerobic exercise is beneficial to a lot of systems in the body, but there is little evidence that it protects us from bone loss.

Our bones are in a constant flux of being broken down by cells called osteoclasts and being built up again with osteoblasts. Strength training places stress on the bones, triggering the activity of osteoblasts and inhibiting osteoclasts, helping us to maintain, and even build, denser bones. This significantly lowers the risk of osteoporosis, which causes around 1.66 million hip fractures globally every year

If that weren't enough to convert you to boot-camp classes over going running, building muscle can also boost your brain. Several studies show that people with a better grip strength – hence better overall body strength – score higher on tests of memory and reaction time, as well as on assessments of verbal and spatial abilities. This means that grip strength can be used as a marker of cognitive decline.

It seems there is something special about muscle training specifically, rather than exercise in general. For instance, older women who lifted weights once a week for a year had significant improvements in cognitive tests of attention, compared with women who performed balance and toning classes.

The underlying mechanisms aren't fully understood, but strength training seems to trigger the release of several brain chemicals, including one called BDNF, that support the health of neurons, helping them to communicate, grow and resist age-related decline, all contributing to a healthier brain.

What's the best way to reap the benefits? There is no easy answer because the type of strength exercises a person can do will differ wildly depending on their age and circumstances. Also, like most things in life, a balance of activities is best. Most studies point to a combination of aerobic and strength exercises being better than either alone. The heart, for instance, responds to both strength and aerobic training, but the two kinds of exercise cause it to structurally adapt in different ways. And remember that many aerobic activities which get the heart rate up, such as circuit training and dancing, are also good for muscle strength.

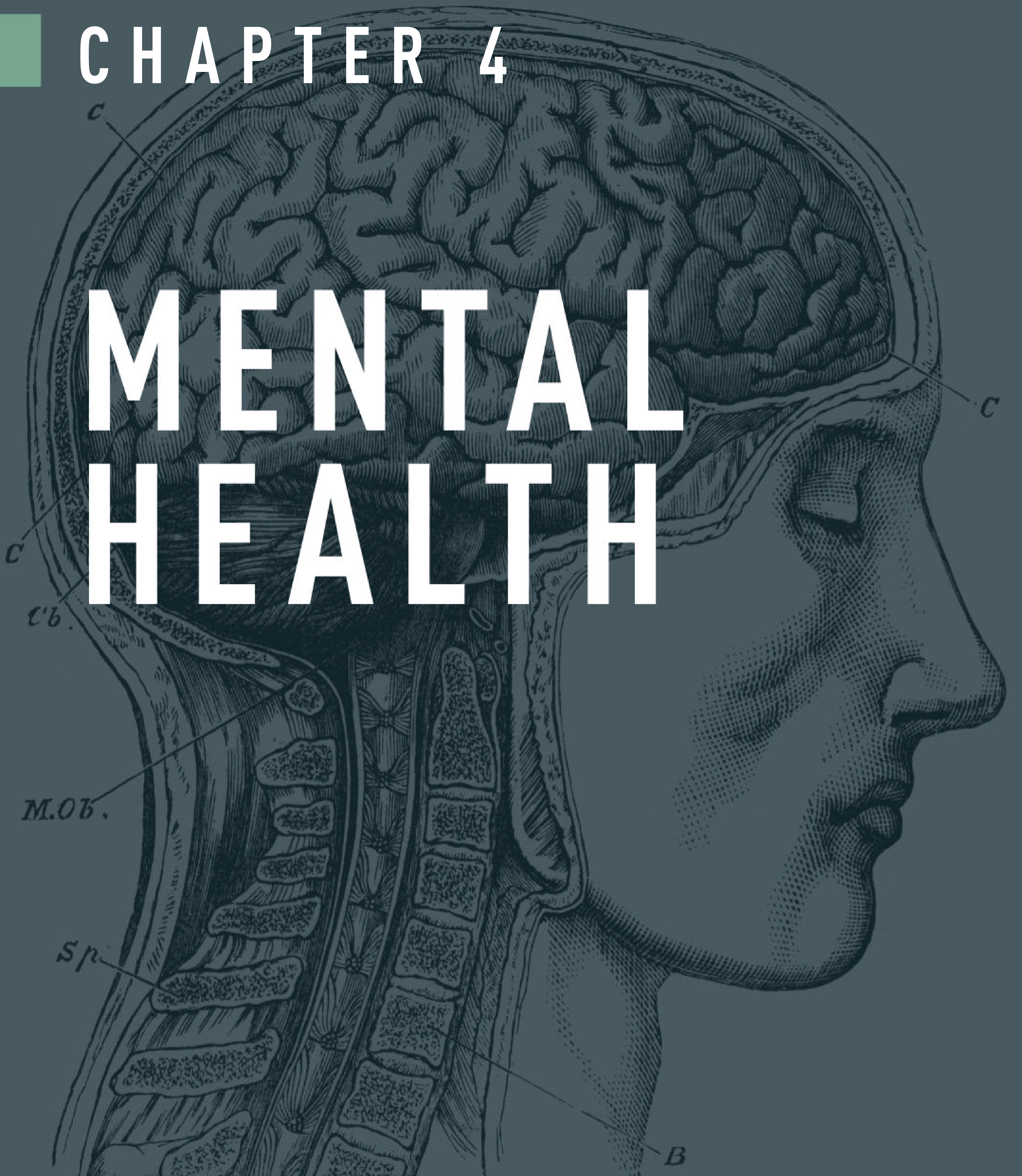
That said, the American College of Sports Medicine has issued some simple advice: it says that adults should perform strength exercises on all major muscle groups – legs, hips, back, abdomen, chest, shoulders and arms – at least twice a week.

That advice comes from evidence that your first workout of the week will give you the most benefit compared with nothing at all. Your second workout will give a bit more benefit, as will the third, but then the results plateau.

Don't get too carried away in the details of what you are doing in these sessions: Provided you exercise a particular group of muscles until they're tired, it doesn't really matter how heavy the weight is or how many times you lift it. The most important thing is that you lift it at all. ▮

CHAPTER 4

MENTAL HEALTH



Mental health conditions such as depression, anxiety and schizophrenia are shockingly common, affecting perhaps 1 in 4 of us at some point in our lives. Meanwhile the rise of neurodegenerative diseases such as Alzheimer's is itself a worrying trend in many ageing populations.

Recent research gives some cause for optimism, however. The discovery that many mental health conditions may be related to one another gives new perspectives on how to tackle them. And while the problem of Alzheimer's is far from solved, we have new clues on what we can do to combat it. In general, the mantra "a healthy mind in a healthy body" rings very true.

MANY CONDITIONS, ONE CAUSE

For decades, mental health problems have been viewed as separate conditions, each requiring a specific and tailored treatment. But there is growing and compelling evidence that they may all share an underlying cause. This realisation could radically change how we diagnose and treat mental illness, putting more focus on symptoms instead of labels and offering more general treatments. It could also explain puzzling patterns in the occurrence of these conditions in individuals and families.

MORE than a century ago, British psychologist Charles Spearman noted that children's performance on one kind of mental task, say verbal fluency, was correlated with their mental skill in other areas, such as mathematical reasoning, spatial manipulation and logic. In other words, children who are good at one thing tend to be good at another, while those who struggle in one area tend to struggle in others. Using a statistical tool called factor analysis, Spearman showed that this is because these different mental abilities are all linked to an overarching cognitive capacity, which he named general intelligence, or the g factor.

Today, applying the same approach to mental health diagnoses has provided the first hints that something similar might be going on. There are a wide range of mental health conditions that manifest with different behavioural and psychological symptoms. Like cognitive skills, they cluster together in individuals, either at the same time or one after another. In 2012, Benjamin Lahey at the University of Chicago and his colleagues analysed information on such diagnoses among 30,000 people studied over three years. Using factor analysis, they found that the observed patterns of illness were best explained by a general tendency towards mental health conditions.

The following year, Avshalom Caspi and Terrie Moffitt at King's College London used information from a thousand people whose health had been ›

DANIEL STOLLE

tracked for four decades since their birth in the early 1970s and got the same result. They coined the term “p factor” to describe an individual’s broad susceptibility to mental health problems. This means that once you have one kind of mental disorder, you’re at greater risk of developing others.

The p factor can also explain puzzling patterns of mental health conditions within families. It had long been known that these conditions have a genetic basis and are highly heritable, meaning they can be transmitted from parent to offspring. Huge twin studies have estimated the heritability of schizophrenia, for example, at nearly 80 per cent, and major depression at about 45 per cent. But having a parent or sibling diagnosed with a given condition doesn’t just increase the odds that you will experience it. It also increases the likelihood that you will be diagnosed with a different condition. For instance, if a parent has schizophrenia, your risk of developing bipolar disorder doubles, and vice versa. That makes sense if you inherit not just a risk for one kind of condition, but a more generalised risk: the p factor.

Indeed, the application of genetics to psychiatry in the past decade has provided key support for the existence of the p factor. In the early days, psychiatric genetics mostly entailed a hunt for individual genes conferring significant risk for developing certain conditions. But this so-called candidate gene approach hit the skids, until SNP analysis came along.

SNP (pronounced “snip”) chips, which look a bit like the memory card in a digital camera, allow scientists to use a small DNA sample to scan someone’s genome and discover which genetic variants they carry. Everyone has millions of single-letter differences in DNA’s four-letter code: where one person has a T, for example, another might have a G (and someone else could have A or C). More than 10 million of these single-nucleotide polymorphisms (SNPs) have been identified, and a single SNP chip can detect a million or more of them in one go.

The breakthrough for the p factor idea came a few years before Moffitt and Caspi coined the term. In 2009, the International Schizophrenia Consortium used SNP chips to genetically analyse more than 3000 people diagnosed with the condition. Instead of pulling out one or a few genetic variants with big impacts on schizophrenia susceptibility, the analysis found the condition was linked to thousands of variants, each having a small effect. Intriguingly, these same variants also increased the risk of bipolar disorder.

Later, this kind of analysis was extended. In 2013, an international group called the Psychiatric Genomics Consortium completed a landmark study. Scientists analysed genomic data from more than 30,000 people diagnosed with conditions including bipolar disorder, major depression or schizophrenia. Again, genetic risk variants cut across the traditional diagnostic boundaries of psychiatry.

Tellingly, the story is very different for neurological conditions – those which affect the nervous system itself, such as Alzheimer’s, Parkinson’s, Huntington’s and multiple sclerosis. A 2018 study from the Brainstorm Consortium based at Harvard University examined genetic data from more than 265,000 people with one of 25 psychiatric and neurological conditions. This revealed that neurological conditions have little or nothing genetically in common with each other or with psychiatric conditions, making them a much better fit for the classical medical model. For neurological conditions in which single genes play a big role, people can be divided into two groups: those who carry the risk variant and those who don’t.

The picture is much messier for mental health conditions. The thousands of SNPs underlying them follow a bell-shaped distribution, meaning that a small percentage of people have very few risk variants, a small percentage have a lot, and most people fall somewhere in between, with symptom severity roughly tracking this curve.

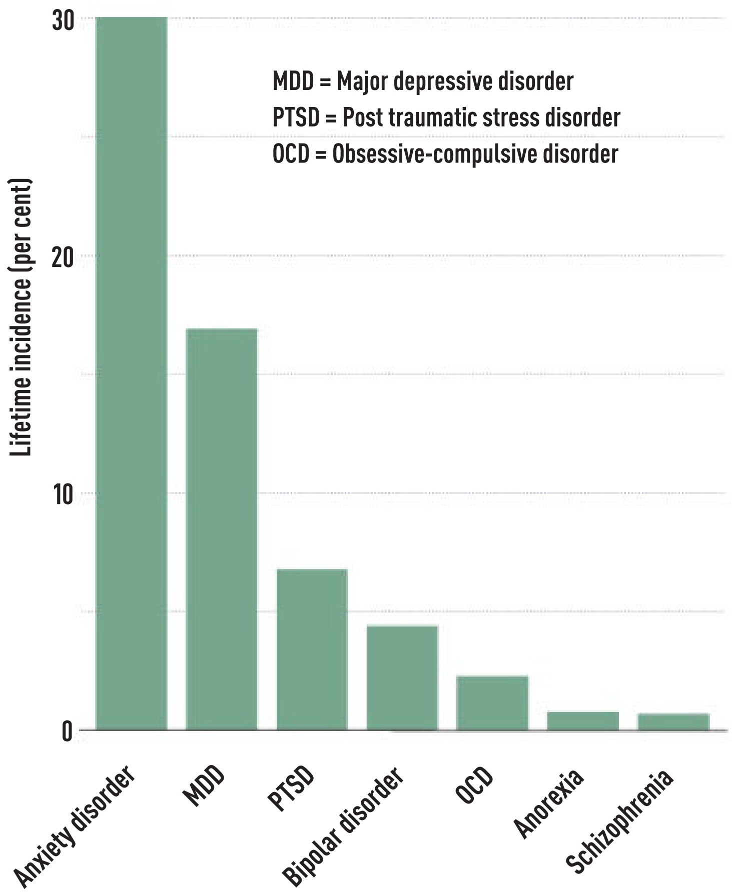
But it gets even more involved. Researchers are now discovering some SNPs which are associated with individual mental health conditions, and that may influence the symptoms people experience. Although there may be a huge genetic overlap between these conditions, the p factor doesn’t explain everything.

There is also more to the story than genes. Researchers have long known that environmental and social factors contribute to mental illness, but remarkably, these also seem to overlap. Child abuse of any kind, traumatic experiences during childhood , and drug and alcohol abuse are all contributing factors.

Robert Plomin at King’s College London and his

HOW COMMON ARE MENTAL HEALTH CONDITIONS?

Around a quarter of people in the UK experience mental health problems each year, with anxiety and depression being by far the most prevalent diagnoses



SOURCES: CDC, HARVARD MEDICAL SCHOOL
DOI.ORG/GD4B88, DOI.ORG/DZVQFW

colleagues recently attempted to quantify the genetic component of the p factor. Drawing on information from more than 7000 pairs of twins, they estimated that genetic differences explain a little over 30 per cent of the variation between people's general susceptibility to mental health problems, with the rest being driven by non-genetic factors. The study also showed that the p factor is stable across a person's lifetime.

Despite these complications, there is growing recognition that mental health conditions have a shared genetic basis. The race is now on to discover how these shared genetic factors manifest themselves biologically. Already, there are hints that many of the implicated genes control activity at the junctions between neurons. In other words, the p factor seems to have something to do with communication between brain cells.

The latest research is even more enlightening. Maxime Taquet at the University of Oxford and his colleagues believe they have identified a "vulnerability network" in the brains of children at high genetic risk of developing mental health conditions. Comparing their brain scans with those of children with a low genetic susceptibility, the team found large differences in three key areas: a structure called the default network that is active while the brain is at rest, a second structure involved in planning and control, and the part of the brain that processes vision.

In a similar study, Caspi and Moffitt found that people with a higher p factor have differences in a brain circuit crucial for monitoring and processing information so it can be used in higher cortical functions such as regulating emotions, thoughts and behaviours.

It is still something of a mystery how having a brain with these sorts of features might influence an individual's psychology. Caspi and Moffitt think that a high p factor probably manifests as a combination of disordered thinking, difficulties regulating emotions and a tendency towards negative feelings. However, even if these links aren't yet clear, the p factor idea may be useful for diagnosing and treating mental health conditions.

Already, psychiatrists sometimes use drugs which were developed to treat one mental health condition to treat another. Antipsychotics, for example, are useful not only in psychosis, but in mania, delirium, agitation, and other conditions. The p factor helps explain why they work. If researchers can unpick the mechanisms involved, they may be able to develop therapies that work better across multiple disorders.

The existence of the p factor could also prompt a shift from treating the conditions themselves to treating the distressing symptoms people often experience. So, even though someone might seek help for depression, they would be provided with the tools and skills to cope with other symptoms when they arise, as well as depressive ones.

Plomin goes even further. For him, these recent insights demolish the orthodox view of mental illness. At the moment, someone seeking help for psychiatric symptoms will be evaluated to determine which of the hundreds of conditions listed in psychiatry's classification bible, the Diagnostic and Statistical Manual of Mental Disorders, best fits their symptoms. This implies there are mentally ill people, versus normal people, he says: "Really we're all somewhere along a continuum." ▮

WHEN STRESS TIPS INTO ANXIETY

Stress and anxiety are often intertwined in our minds, but they refer to different things. Stress is a biological process that helps us to focus on a challenging situation and adapt our behaviour. Anxiety can be triggered by stress, but it is a feeling that tends to hang around after the initial threat or challenge disappears. If anxiety occurs most days for longer than six months, it is known as generalised anxiety disorder.

ANXIETY disorders – generalised anxiety, panic attacks, social anxiety and phobias – are the most prevalent mental health problem in the US and Europe. A growing number of reports suggest they could be a global concern. In the West, they cost healthcare systems more than $40 billion each year. On average 1 in 6 of us will contend with an anxiety disorder at some stage in our lives.

The damage is real. Anxiety disorders have been linked to depression and increased substance abuse, particularly of alcohol. A recent study found that men who have anxiety disorders are twice as likely to die from cancer as men who don't, even when factors such as drinking and smoking are taken into account.

Unlike stress, which normally occurs within a discrete time frame, anxiety sticks around. If it starts interfering with someone's day-to-day life, or causes a lot of distress, they may be diagnosed with an anxiety disorder. "Maladaptive beliefs" are a hallmark of these disorders, In social anxiety disorder, the most common type, you might believe that blushing will result in people laughing at or shunning you. People with this type of disorder experience persistent and overwhelming fear around social interactions.

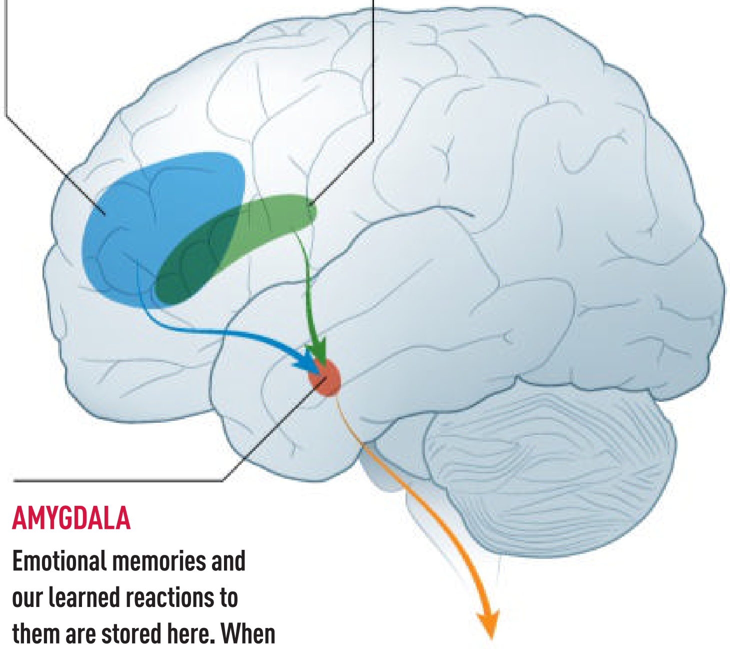
←
Turn back to page 24 for more on the stress response

If you have panic disorder, you might assume that you are having a heart attack if your heart starts to race. The physical symptoms of anxiety – a pounding heart, difficulty breathing, feeling dizzy or flushed – will then come on in a rush. Everyone can experience such panic attacks from time to time. In panic disorder, the attacks are regular and become a source of anxiety themselves.

Generalised anxiety disorder, meanwhile, is characterised by chronic worrying about a range of different events or activities, for at least six months. The belief driving your anxiety can, for example, be the feeling it's your job to take care of other people, or that you have responsibilities that you must meet at all cost. It's still too early to say what effects the coronavirus will

THE ANXIOUS BRAIN

The walnut-sized amygdala is responsible for initiating the fight-or-flight response. Two circuits feed into it, one that enhances its activity and one that dampens it. In people with anxiety disorders the normal workings of these circuits are disturbed, and the amygdala is hyperactive



PREFRONTAL CORTEX
Centre for rational, logical thought. It is involved in laying down new memories and tempering learned fear responses

PREFRONTAL AND ANTERIOR CINGULATE CORTEX
Amplifies negative information in your surroundings and makes you pay attention to it

AMYGDALA
Emotional memories and our learned reactions to them are stored here. When active, it triggers the release of hormones responsible for the fight-or-flight response

Fight-or-flight response (sweaty palms, racing heart etc)

have on such disorders, but the betting is it won't have improved things for those susceptible.

Although we are still a long way from fully understanding what is going on in an anxious brain, recent studies offer some insights. Central to it all is the amygdala, the brain region we've already encountered in our discussions of stress that processes emotions and triggers the release of the fight-or-flight hormones. The amygdala is linked to parts of the brain that process social information and help us make decisions. During bouts of anxiety, this brain circuit switches on and then off again, but in people with anxiety disorders it seems to get stuck in the on position. Possibly, it is amplifying negative environmental information and triggering an ongoing fight-or-flight response. Besides causing rapid heart rate and breathing, a dry mouth, shaking and tense muscles, this has less obvious effects, like slowing digestion and making us more susceptible to pain.

Like many other mental health conditions, genes are involved. A recent study of more than 106,000 people identified nine regions of the genome that seem to correlate with neuroticism, or proneness to anxiety. Some of these contain genes previously linked to anxious behaviour, such as CRHR1, which regulates release of the stress hormone cortisol. The same gene has also been associated with anxiety-related behaviour in mice, and panic disorder in humans.

Age and biological sex also seem to matter. The prevalence of most anxiety disorders peaks in 18 to 34-year-olds before dropping off again. Specific phobias were the exception, peaking in 35 to 50-year-olds. And population studies show that women are about twice as likely to develop an anxiety disorder as men. In part, this may be down to hormones and their influence on the brain. The surges in oestrogen and progesterone that occur during pregnancy, for instance, have been linked to obsessive compulsive disorder, an anxiety-related condition. There may be other explanations too, such as the fact that women tend to cope with stressful situations differently: they tend to worry a lot more about what's going to happen, whereas men tend to take a more problem-focused approach.

Modern life may be packed with events outside your control, seemingly designed to foster anxiety and self-doubt. The important thing is to recognise the symptoms and do something about them. ▮

HOW TO KEEP YOUR BRAIN YOUNG

Studies are cruelly consistent: by the age of 45, our basic cognitive abilities begin to slip, and as we get older, the crucial brain regions involved in memory, attention and perception shrink and no longer communicate with one another as efficiently as they once did. You may find that you aren't quite as quick as you once were. It takes longer to recall where you left your keys, more effort to help your kids with their maths homework.

This doesn't necessarily mean you'll get dementia. Getting older slows us down, but the human brain can stay sharp well past 100 years of life, and when healthy older people are given extra time to perform cognitive tasks, the results are usually on par with younger folks. Even if you do receive a diagnosis of dementia, there are plenty of science-backed strategies for keeping your brain fitter for longer. And it is never too late to begin.

WITH life expectancy continuing to rise and the baby-boomer population bulge standing on the cusp of old age, Western countries face what is sometimes called a looming tsunami of dementia. The epidemic will place huge strain on healthcare systems; in the UK, the annual cost of caring for someone with this condition is more than the average salary. And on a personal level, the prospect of a long life loses its appeal if it ends this way.

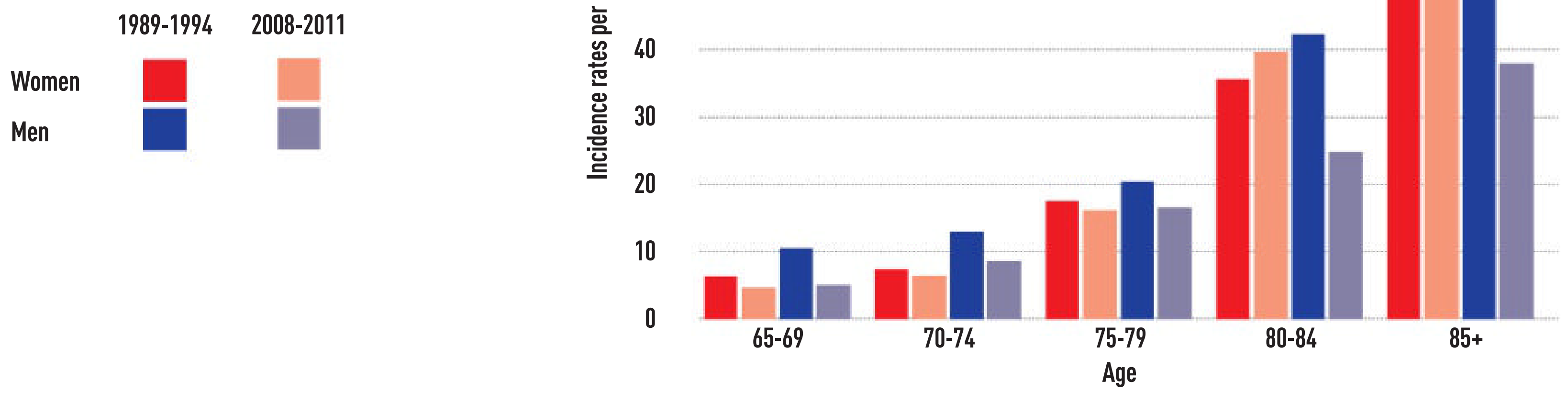
But wait a minute. All the gloomy predictions have been based on a central assumption that people will continue to develop dementia at the same rate as they always have. It is a reasonable assumption – age is the primary risk factor for dementia – but it may well be wrong. There is emerging evidence that the dementia rate in developed countries has fallen.

Dementia is a general breakdown of the intellect and personality, with disintegration of memory, attention and emotional control. About two-thirds of dementia cases are caused by Alzheimer's disease, in which neurons die off amid distinctive clumps of protein. The next most common form is vascular dementia, caused by deterioration of the brain's blood vessels and often involving minor strokes. There are other, less common subtypes, plus a growing belief that dementia at very old ages typically involves a mix of different forms of disease.

What's always been known is that the risk of dementia rises markedly with age – seemingly

BEATING BACK DEMENTIA

In the UK, improvements in education and heart health may have helped reduce dementia rates, although women remain more vulnerable – largely because they live longer



inexorably. Very few cases occur before the age of 60, and between 60 and 70 the condition is still restricted to an unlucky 1 per cent or so. After this point, though, the odds worsen significantly: about 5 per cent of 70 to 80-year-olds are affected, and beyond 80 the risk rises ever more sharply.

The logic has always seemed inescapable: the more 80-year-olds there are around, the more people there will be with dementia. The number of people with dementia globally is often predicted to triple by 2050.

But over the past few years there have been hints that the actual numbers don't fit this picture, and dementia might in fact be on the retreat. Between the late 1980s and 2011, the proportion of people over 65 with dementia actually dropped by 20 per cent in England and Wales. Between 2000 and 2012, dementia rates in that age group dropped by 24 per cent in the US. Similar declines have been reported in other developed countries.

There are two driving factors: The first is better control of conditions such as high blood pressure and diabetes which can damage the brain's blood vessels. The second is a rise in educational attainment.

After the second world war, there was an increase in schooling that averaged out to about an extra year of education across the US population. Research suggests that people with more education, or those who have done things like learn a new language or learn to play a musical instrument, may be resilient to symptoms of dementia. That doesn't mean they escape the ravages of vascular dementia or plaques of Alzheimer's, but they may cope better with the damage because they have a greater amount of mental padding, or "cognitive reserve".

Increased cognitive reserve is thought to help in two ways: boosting the brain's ability to work around damaged areas, and promoting more efficient processing. That might also explain why people with more education seem to decline so rapidly: it's not that Alzheimer's comes on suddenly, it's that by the time symptoms manifest the disease may already be quite advanced.

It is important to acknowledge that much of dementia risk is down to genetics: about 70 per cent in the case of Alzheimer's disease. "We know that some people have strong genetic risk factors that can predispose them to some forms of dementia whether they live a healthy lifestyle or not," says Jonathan Schott of the Dementia Research Centre at University College London.

However, if 30 per cent or more of dementia risk is down to lifestyle and environmental factors, there is still an opportunity to make a difference.

Physical activity may be most critical. Exercise increases the production of a chemical called brain-derived neurotrophic factor. Sometimes referred to as brain fertiliser, it spurs the creation of neurons in the hippocampus, a part of the brain that helps consolidate memories, and new connections between them. It also boosts the number of mitochondria, the energy factories of cells, inside the brain. Together, these changes seem to bolster the brain against dementia and Alzheimer's disease. A hormone called irisin, which is generated by muscle tissue during exercise, may also play a role. Fernana de Felice at the Federal University of Rio de Janerio and colleagues found that people with Alzheimer's had lower levels of the hormone compared with healthy individuals. In tests with mice, the

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team could induce learning and memory deficits by cutting out irisin and could reverse the effects by restoring the hormone. When irisin signalling was blocked in mice with a rodent version of Alzheimer's, the brain benefits of physical exercise were lost.

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For more on the benefits of exercise, see page 51

It's not just physical exercise that makes a difference. The brain is often likened to a muscle, and for good reason: give it a good workout and it will stay strong. A few years ago, headlines were full of claims about brain-training apps and computer games that offered a shortcut to improved cognitive fitness. But these have largely been debunked. Instead, the trick seems to be to find activities that boost cognitive reserve.

There seems to be something particularly special about music and language. For instance, people who played an instrument as a child, even for a few years, tend to be protected later in life from decline in the brain areas associated with hearing. And people who speak more than one language develop dementia later, on average, than monolinguals. A 2018 study found that musical training and speaking a second language both help the brain work more efficiently, requiring less energy to accomplish the same cognitive tasks. Music to our ears.

Another option is to be socially active. For instance, being married is strongly associated with a reduced risk of cognitive decline and dementia – possibly because of regular conversation and the effort involved in maintaining a good relationship between spouses. People who report feeling that their life has a sense of direction and purpose also appear to perform better when given memory and cognitive tasks. This could be because activities such as volunteering with local organisations, or helping to raise grandchildren, help keep people socially and physically active.

Finally, there's diet. We've talked earlier on about the benefits of the "Mediterranean" diet, which recommends eating plenty of fruit, vegetables, whole grains and olive oil. It does seem to keep us healthy, cutting the risk of heart disease and early death. But recently a few studies have begun to suggest it can stave off cognitive decline too. ▮

CAN GUM DISEASE CAUSE ALZHEIMER'S?

In 2016, researchers discovered that the sticky amyloid plaques whose buildup is associated with Alzheimer's disease (see next article) seem to function as a sticky defence against bacteria. They found that the protein can act as an anti-microbial compound that kills bacteria. When they injected bacteria into the brains of mice engineered to make Alzheimer's proteins, plaques developed round bacterial cells overnight.

At the time, the team said it still believed that amyloid itself went on to cause the brain damage of Alzheimer's, not bacteria. But a spate of subsequent studies have looked at microbes, and suggested an alternative hypothesis. Bacteria have been found in the brains of people who had Alzheimer's when they were alive. But it hasn't been clear whether the bacteria caused the disease or were simply able to enter brains damaged by Alzheimer's.

Multiple teams have been researching *Porphyromonas gingivalis*, the main bacterium involved in gum disease, which is a known risk factor for Alzheimer's. So far, teams have found that *P. gingivalis* invades and inflames brain regions affected by Alzheimer's; that gum infections can worsen symptoms in mice genetically engineered to have Alzheimer's; and that it can cause Alzheimer's-like brain inflammation, neural damage and amyloid plaques in healthy mice. It's still early days, but it's yet another reason to keep good care of your teeth.

LIGHTFIELDSTUDIOS/ISTOCK PHOTO

ESSAY: MATTHEW WALKER

SLEEP AND ALZHEIMER'S

It is becoming increasingly clear that getting enough sleep is vital for our physical and mental well-being. This is also true of our long-term brain health: even a single night of poor sleep can cause changes in the brain implicated in Alzheimer's disease. So, what steps can we take to improve our sleep? Sleep scientist Matthew Walker explains.

I DON'T mean to pry, but how much sleep did you get last night? What about over the past week? I ask because the answer could have serious consequences for your future mental health.

More than 44 million people worldwide currently have Alzheimer's disease, including members of my own family. The health, economic and personal impact is staggering. There has been a marked acceleration in the number being diagnosed with the disease as the human lifespan has increased, but also, importantly, as total sleep time has decreased.

As a sleep scientist, I became interested in this connection some years ago. What I have found is striking. Not only does sleep disruption play a role in the declining mental abilities that typify Alzheimer's disease, but getting enough sleep is one of the most important factors determining whether you will develop the condition in the future.

As we age, our sleep gets worse. This is especially true for the quality of our deep, non-rapid eye

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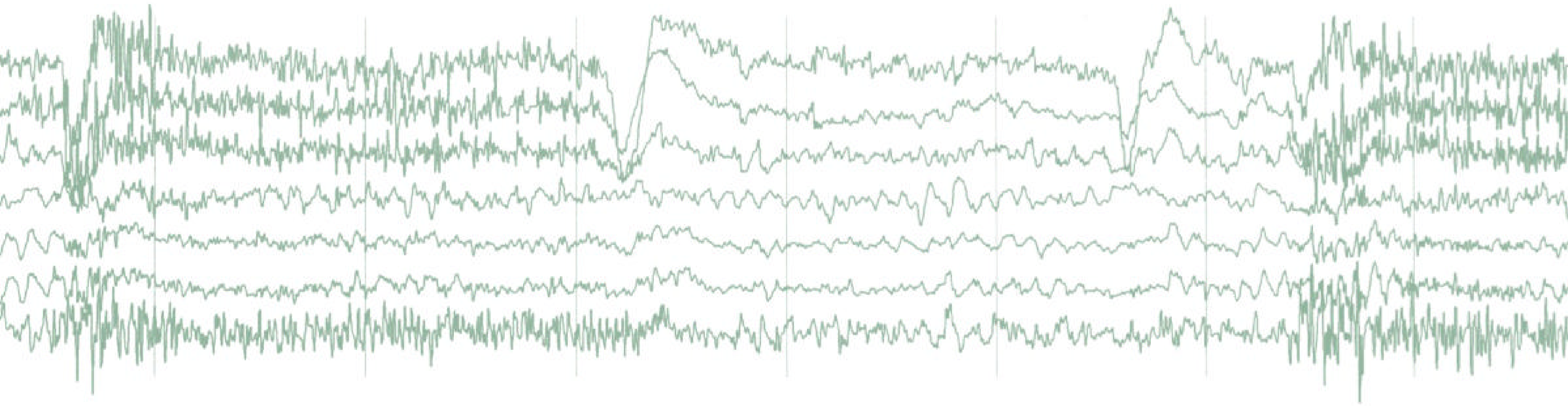
PROFILE MATTHEW WALKER

Matthew Walker is professor of neuroscience and psychology at the University of California, Berkeley, and author of the bestselling book *Why We Sleep*



movement (NREM) sleep. Unfortunately, this is the very type of sleep that we now know helps fix new memories into the architecture of the brain, preventing you from forgetting.

But if you assess a patient with Alzheimer's disease, the disruption of deep sleep is exaggerated. More telling, perhaps, is the fact that sleep disturbance precedes the onset of Alzheimer's by several years, suggesting that it is an early warning sign of the condition – or even a contributor. After diagnosis, the magnitude of sleep disruption progresses in lockstep with the severity of the symptoms, further suggesting a link between the two.

However, it was only recently that we realised this relationship is more than just a correlation. While much remains to be understood, we now recognise that sleep disruption and Alzheimer's interact in a cycle that can initiate and accelerate the condition.

Alzheimer's disease is associated with the build-up of a toxic form of protein called beta-amyloid, which aggregates in sticky clumps, or plaques, within the brain. Amyloid plaques are poisonous to brain cells, impairing their function and ultimately killing them. What is strange, however, is that amyloid only attacks some parts of the brain and not others, the reasons for which remain unclear.

What struck me about this very selective pattern is the location in the brain where amyloid plaques accumulate early in the course of Alzheimer's disease, and most severely in the late stages: the middle part of the frontal lobe. This brain region is essential for the electrical generation of deep NREM sleep.

Back in 2007, I wondered whether the reason Alzheimer's patients have such impaired deep NREM sleep was, in part, because the disease erodes the very region of the brain that normally generates this key stage of slumber. At my sleep research centre at the University of California, Berkeley, we set about testing this idea.

A decade later, having assessed the sleep of hundreds of people between 65 and 90 years of age with varying degrees of amyloid build-up in the brain, we have arrived at the answer: the more amyloid deposits there are in the middle regions of the frontal lobe, the more impaired that person's deep-sleep quality – specifically, the disease is robbing people of the very deepest slow brainwaves of NREM sleep.

With that in mind, part of my research is now focused on diagnostics. In particular, we want to know if that specific "dent" in sleeping brainwave activity can be used to spot those people at greatest risk of developing Alzheimer's years or even decades in advance. If sleep does prove to be an early warning sign – especially one that can be spotted relatively cheaply, non-invasively and for large numbers of people, unlike with brain scans – then early intervention becomes possible.

Building on these findings, we began to look at another missing piece in the puzzle of Alzheimer's disease: how does the build-up of toxic plaques contribute to memory loss?

We already knew that in young healthy adults, the slow brainwaves of deep NREM sleep effectively hit the "save" button on new memories, helping us retain what we have recently learned. Sleep also helps

> **“In Alzheimer’s patients, the disruption of deep sleep is exaggerated”**

us access and thus remember past experiences. If amyloid was blocking deep NREM sleep in Alzheimer’s disease, then perhaps this loss of youthful deep sleep prevents older adults from being able to save new memories and hold on to experiences past?

To test this idea, we had elderly Alzheimer’s patients with varying levels of amyloid in their brains learn a list of new facts in the evening. The next morning, after we had recorded their sleep in the lab during the night, we tested the individuals to see how effective their sleep had been at cementing and thus holding on to those new memories.

We found that those with the highest levels of amyloid deposits in the middle frontal regions of the brain had the most severe loss of deep sleep and, as a consequence, failed to successfully “save” those new memories. Overnight forgetting, rather than remembering, had taken place. The disruption of deep NREM sleep is therefore a hidden middleman brokering the bad deal between amyloid and memory impairment associated with Alzheimer’s disease.

However, this was only half of the story. Our work had shown that the amyloid plaques of Alzheimer’s disease may be associated with the loss of deep sleep. But can a lack of sleep actually cause amyloid to build up in your brain, and directly increase your risk of developing Alzheimer’s disease?

Around the time that we were conducting our studies, Maiken Nedergaard at the University of Rochester, New York, made one of the most spectacular discoveries in the field of sleep research in recent decades. Working with mice, she found that a kind of waste network called the glymphatic system exists within the brain, composed of glial cells that position themselves around the neurons that generate electrical impulses. Just as the lymphatic system drains contaminants from your body, the glymphatic system uses cerebrospinal fluid to collect and break down harmful metabolic debris generated by the hard work of your neurons.

Although the glymphatic system is somewhat active during the day, Nedergaard and her team discovered that it is during deep NREM sleep that this sanitisation system kicks into high gear. With the pulsing rhythm of deep NREM sleep, the brain expels 10 or 20 times more effluent. Consider it a night-time power cleanse of sorts.

She also discovered that during deep NREM sleep, the brain’s glial cells were shrinking in size by an astonishing 60 per cent. That created greater space for the cerebrospinal fluid to clean out the metabolic refuse.

What does this have to do with Alzheimer’s disease? Nedergaard showed that one piece of toxic debris washed away by the glymphatic system during sleep is amyloid protein – the very damaging element associated with Alzheimer’s disease. That finding fitted with another remarkable discovery. David Holtzman at the University of Washington in St Louis and his team prevented mice from getting deep NREM sleep, keeping them awake instead. They saw an immediate increase in the amount of amyloid in the rodents’ brains.

Of course, there are some significant differences between mice and humans. Is the same really true if we skimp on our sleep? Alarmingly, in July, Holtzman showed this to be so. His team deprived otherwise healthy adults of their deep NREM sleep, but kept total sleep time the same. To do this, they waited until the subjects entered this phase of sleep and then played sub-awakening sounds that would lift the brain out of deep sleep, but not wake them up. The next day, they measured the amount of amyloid within the volunteers' spinal fluid. Without the cleansing benefit of deep NREM sleep, they found a significant escalation of Alzheimer's-related amyloid.

Numerous epidemiological studies also suggest that getting too little sleep across your lifespan will significantly raise your risk of developing Alzheimer's disease. This is true regardless of whether you are already predisposed to getting it. You are at even higher risk if you have an untreated sleep disorder such as insomnia or sleep apnea. Simply put, sleep is our neurological salvation – or, perhaps, sanitation.

Invert these findings, however, and a radically hopeful prediction emerges. By improving someone's sleep, we should be able to reduce their risk of developing Alzheimer's disease – or at least delay it.

Early support for this idea has emerged from clinical studies with middle-aged and older adults who have sleep disorders, but have not yet transitioned into Alzheimer's disease. When their sleep problems were successfully treated, their rate of cognitive decline slowed, delaying the onset of Alzheimer's by up to 10 years.

So improving sleep quantity and quality helps battle back the approaching onslaught of the disease. But what about those individuals for whom sleep is difficult, or due to ageing and dementia, physiologically not possible? Medication does not appear to be the answer. Current sleeping pills do not produce naturalistic sleep, and are associated with higher rates of mortality and cancer.

My research group is now trying to develop a number of electrical brain-stimulating methods for amplifying deep NREM sleep in older adults and those with

WHAT ELSE SLEEP IS GOOD FOR

Every animal needs sleep. Rats deprived of sleep die within in a month, and people with a rare insomnia disease also die early. A wide range of disorders have been linked to disturbed sleep or sleep deprivation, but we still don't really know what sleep is for.

One theory is that sleep helps us consolidate new memories, but sleep may be important for pruning down the connections between our brain cells, to free up space for future memories.

How much sleep you need is influenced by your genetics. It's good to aim for between 7 and 9 hours every night, but some people may need 10 or be fine after only 6. While it's tempting to flatter yourself, bear in mind that only 3 per cent of people can get by on only 4 to 6 hours' sleep with no problems. It's probably best to aim for a minimum of 7 hours a night, enough time to go through several full sleep cycles.

The first few cycles are important for deep sleep, which appears to be particularly important for brain maintenance – pruning connections between neurons and clearing out unwanted clutter like proteins linked to Alzheimer's disease (see main story). Later cycles include more rapid eye-movement (REM) sleep, which is thought to be vital for learning, and where most dreaming seems to occur.

dementia. Like a support choir to a flagging lead vocalist, we are trying to electrically "sing" in time with weakened sleep brainwaves, artificially boosting their size. We hope that by restoring some deep sleep, we can salvage aspects of learning and memory that have failed in older individuals and those with dementia.

That is treatment, but my goal is prevention. If we are successful in our smaller trials, I aim to develop a method that is cost-effective and can be scaled up to population level for repeat use. The ideal would be to begin supplementing the declining deep sleep of vulnerable individuals during mid-life, many decades before the tipping point where Alzheimer's is inevitable. I admit it is a lofty ambition – even a foolhardy one – but when one sees family members dealing with the disease, it becomes an imperative.

So how do we ensure better quality sleep in the meantime? Most adults need 7 to 9 hours a night, but as we age, the amount of sleep we need changes. An 18-year-old, for instance, might need anywhere between 6 and 11 hours. We are often told that older adults need less sleep, but that's probably not true. They seem to need as much sleep as other adults, but that amount is harder to get as we age.

As a general rule, you shouldn't need to set an alarm to wake up in the morning. If you do, you probably aren't getting as much sleep as you need. What's more, time in bed doesn't equal time asleep. Try aiming for 8 hours in bed for a good night's rest.

You cannot get back that which is lost by way of sleep deficiency in the past. However, it's never too late to change for the future. It can have a profound benefit. For example, treating sleep apnea – a disorder in which people stop breathing and wake up frequently during the night – in Alzheimer's disease patients significantly improves cognitive function. What's more, treating sleep problems in cognitively typical older individuals delayed their ultimate decline into Alzheimer's disease by up to 10 years. There is always the chance for you to prioritise sleep, and in doing so, help ensure a longer and healthier life.

These are five things you can do right now for better sleep. The first is regularity: go to bed and wake up at the same time, no matter what. Even if you've had a bad night of sleep, or it's the weekend. The wake-up time is the most important as this will build up your sleep drive during the day. This is the urge to sleep that is tied to your circadian clock.

Avoid caffeine after 1pm, and no alcohol after 5 or 6pm. As a guide, never go to bed tipsy. Alcohol is a sedative, and sedation is not sleep. Unfortunately, most people mistake one for the other. Alcohol also blocks your REM sleep, and it further fragments it with short awakenings thought the night. You wake up feeling unrefreshed and unrestored when having had a drink in the evening.

Keep your bedroom cool. Your body needs to drop its core temperature by approximately 1.2 degrees Celsius to initiate sleep. This is the reason it's always easier to fall asleep in a room that's too cold than too hot. About 18.5°C is optimal for your bedroom. Cooler than you think. It's fine to wear socks if you get cold feet. But cold it must be.

Also, mind your bedroom lighting. Switch off as many lights as possible in the last hour before bed so as not to interfere with natural production of the sleep hormone melatonin, which is produced in the evening. Tablets and phones in particular generate lots of short wavelength blue light, which reduces melatonin concentrations. So no screen time 1 hour before bed. Blackout curtains are also helpful.

Finally, if you're struggling to fall asleep, don't lie there worrying about it. If it's been longer than twenty minutes or so, get out of bed and do something quiet and relaxing until the urge to sleep returns.

To be clear, insufficient sleep is only one of several risk factors associated with Alzheimer's disease. Sleep alone will not be the magic bullet that eradicates dementia. Nevertheless, prioritising sleep – however old you are –is a clear way of lowering your risk of developing Alzheimer's disease. That's a fact well worth waking up to. ▮

CHAPTER 5

COMBATING CANCER

Of all diseases, cancer strikes fear into the hearts of even the most hardened of us. Most people know someone whose life has been cut prematurely short by this disease.

Its shape-shifting nature also renders it stubbornly resistant to many of the treatments we throw at it. Yet new insights into how tumours evolve are paving the way for better strategies to prevent and treat them.

WHAT CAUSES CANCER?

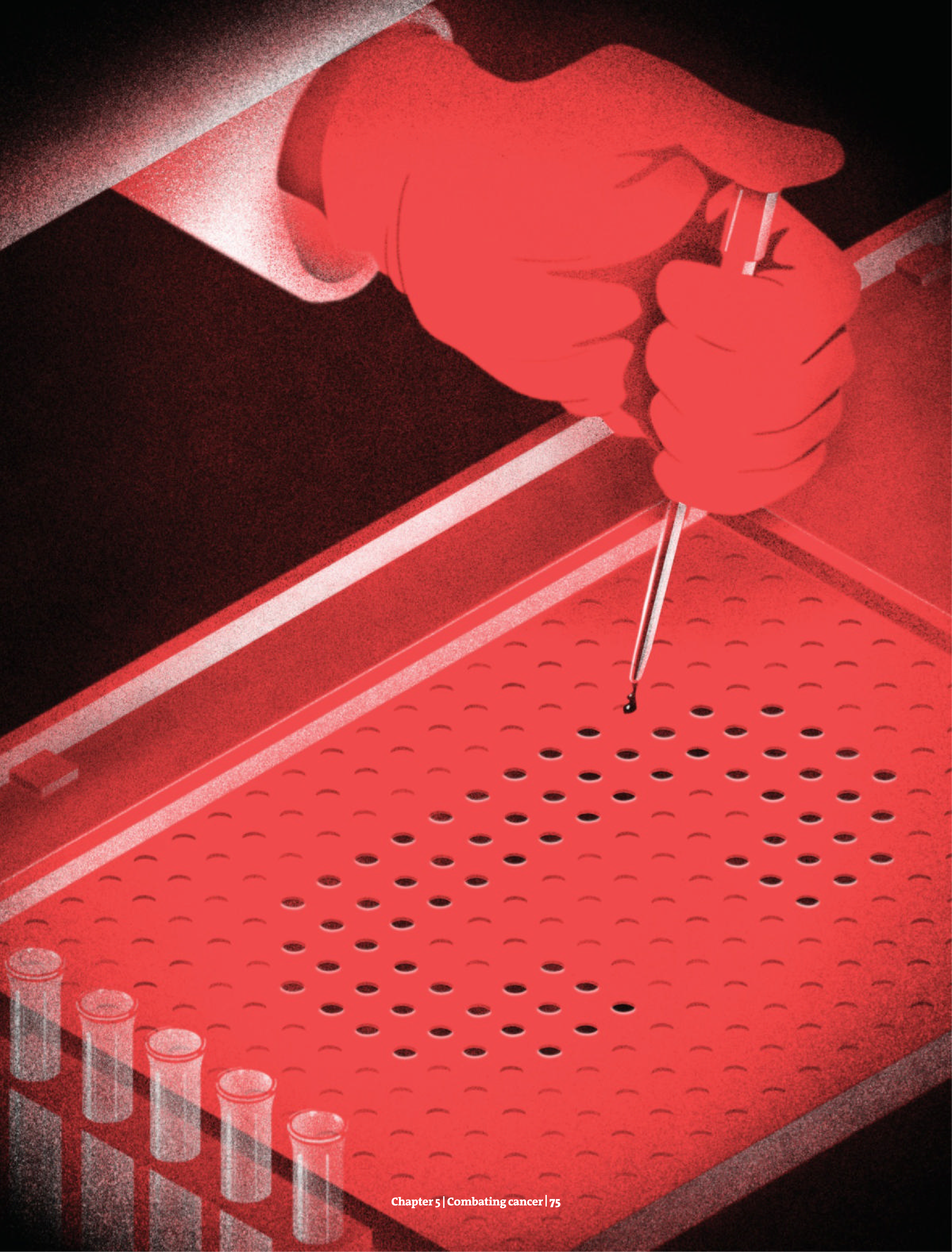
Cancer is not a single disease and its causes are many and complex. Our knowledge about how to reduce our risks has come a long way in recent years, however, thanks to a huge amount of research into both genetic susceptibility and environmental factors that affect cancer risk. So, what do we know – and not know – about the causes of cancer? The most promising line might be to take an evolutionary perspective.

CANCER affects every one of us. Whether or not you have had it yourself, you surely know someone who has. For people in the UK, the lifetime chance of being diagnosed with the disease is 1 in 2. Globally, cancer is second only to cardiovascular disease as a cause of death, killing an estimated 1 in 6 people.

We are bombarded with so much information and misinformation about what might cause cancer that it is often hard to separate myth from reality. The extent of public confusion on the subject was glaringly exposed in a survey of 1330 people in England published last year. Researchers from University College London and the University of Leeds, UK, reported that more than a third of the general public mistakenly attributed carcinogenic properties to artificial sweeteners, genetically modified food, drinking from plastic bottles and using a cellphone. Over 40 per cent thought stress causes cancer, although there is no proven link. More worryingly, only 60 per cent of people believed sunburn can lead to cancer. And only 30 per cent were aware of the strong link between human papillomavirus (HPV) infection and the disease.

When it comes to cancer, the disconnect between people's beliefs and scientific findings has deep roots. Take, for example, the controversy over aspartame. Over the past half-century, this artificial sweetener has been the subject of intense debate, with public opinion waxing and waning about whether it causes brain cancer. There are plenty of internet articles

DANIEL STOLLE



describing aspartame as a carcinogen. Yet there is no conclusive evidence that it can trigger mutations that cause cells to proliferate out of control, which is the hallmark of cancer. The same goes for antiperspirants, water fluoridation, power lines, smart meters, cleaning products and countless other things.

It would be wrong to conclude that we are simply gullible or ignorant. In fact, public opinion isn't always unfounded. The belief that injuries can cause cancer has been rejected as a myth by cancer experts, including the authors of the UCL/Leeds study, yet research published in 2017 indicates that there may indeed be a link. Besides, there is real uncertainty about the carcinogenic properties of various substances.

Take coffee. Last year, a judge in California ruled that all coffee sold in the state should carry a cancer warning because coffee contains acrylamide, which may be carcinogenic. Not long after, California officials rejected the ruling, to the relief of coffee-drinkers everywhere. Yet coffee does contain acrylamide, which the World Health Organization (WHO) describes as a "probable human carcinogen" – despite there being no clear evidence that it increases the risk of any type of cancer in humans. And its presence in fried, roasted and baked foods is the reason we are advised to avoid eating overcooked chips, burnt toast and the like. But whether your morning cup of coffee contains enough to make it a cancer risk isn't known, as there has been insufficient research to settle the matter.

Even where there is a lot of research, results are often open to interpretation. That is partly because both the main approaches to testing potential carcinogens have drawbacks. Laboratory studies using live animals, or their cells, can be rigorous but the results may not apply to humans. Studies in people, meanwhile, are difficult to interpret because many confounding factors influence the results.

Yet, all this confusion belies the fact that there are things you can do to reduce your chances of getting cancer. According to the WHO, around one third of deaths from cancer are due to the five leading behavioural and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol use.

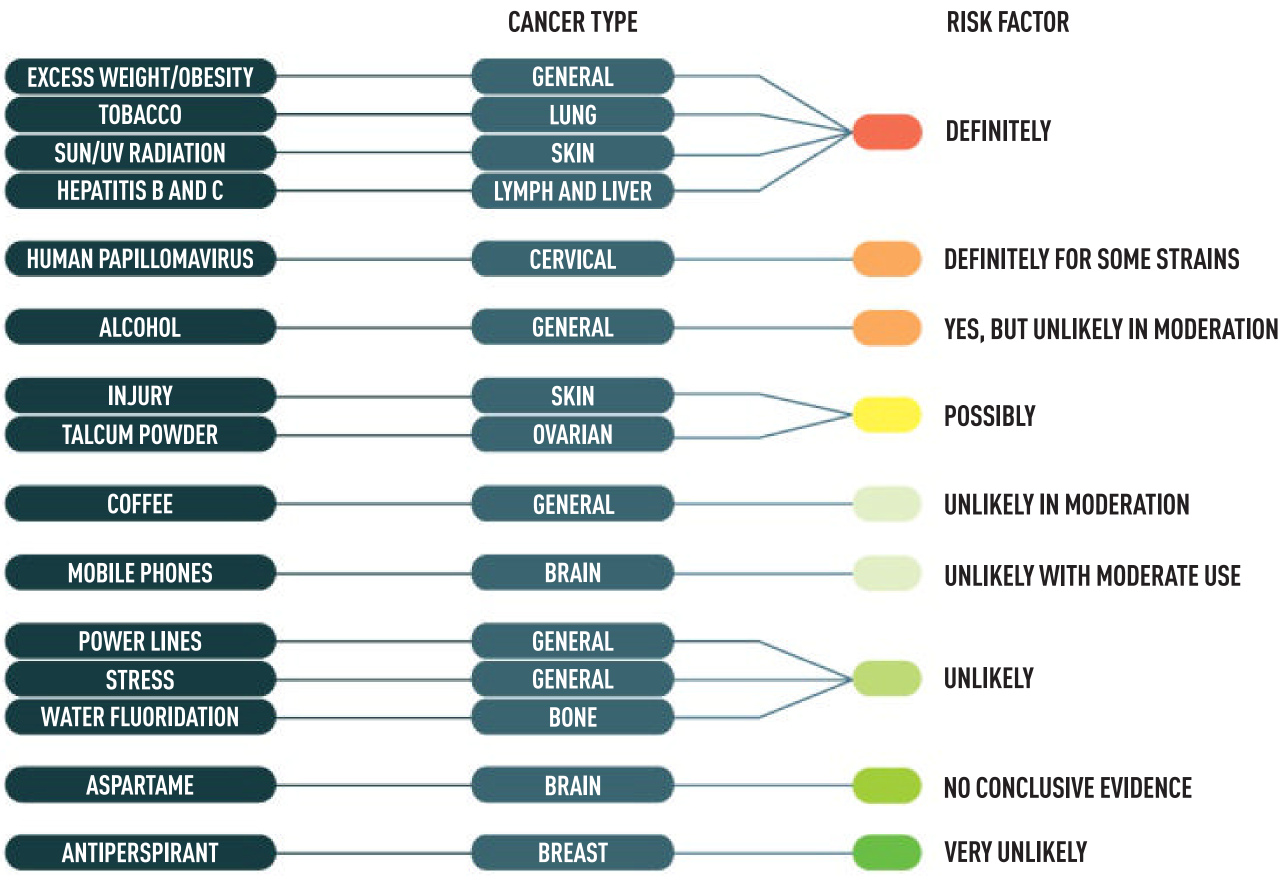
The biggest risk factor is tobacco, which accounts for 22 per cent of cancer-related deaths worldwide. The WHO also singles out exposure to sunlight and other forms of radiation, and notes that cancer-causing infections such as hepatitis and HPV are responsible for up to a quarter of cancer cases in low and middle-income countries.

Admittedly, researchers have homed in on a whole range of carcinogens and it isn't always possible to avoid or reduce our exposure to them. But a bigger problem is that we still have a long way to go to identify all the risk factors for cancer. Recent research found that only about four out of 10 cases are due to a known cause, with smoking and obesity accounting for the majority of these. Another study put the level of uncertainty even higher. It concluded that

RISKY AND NOT SO RISKY

Certain things do increase your chance of getting cancer – but other things you needn't worry about so much

SOURCE: CANCER.ORG



	CANCER TYPE	RISK FACTOR
EXCESS WEIGHT/OBESITY	GENERAL	DEFINITELY
TOBACCO	LUNG	
SUN/UV RADIATION	SKIN	
HEPATITIS B AND C	LYMPH AND LIVER	
HUMAN PAPILLOMAVIRUS	CERVICAL	DEFINITELY FOR SOME STRAINS
ALCOHOL	GENERAL	YES, BUT UNLIKELY IN MODERATION
INJURY	SKIN	POSSIBLY
TALCUM POWDER	OVARIAN	
COFFEE	GENERAL	UNLIKELY IN MODERATION
MOBILE PHONES	BRAIN	UNLIKELY WITH MODERATE USE
POWER LINES	GENERAL	UNLIKELY
STRESS	GENERAL	
WATER FLUORIDATION	BONE	
ASPARTAME	BRAIN	NO CONCLUSIVE EVIDENCE
ANTIPERSPIRANT	BREAST	VERY UNLIKELY

two-thirds of all cancers are consequences of "random mutations" – DNA copying errors that cannot be predicted at present.

With so much effort and money being poured into cancer research, why are we still so ignorant? Well, cancer isn't like most other diseases. For a start, it can develop slowly, making it almost impossible to pinpoint the cause as you can with, say, malaria or cholera. There also isn't a simple link between cause and effect – a person may chain-smoke all their life, for example, and never get lung cancer. In fact, in most cases it is simplistic to think there is a single cause: the uncontrolled division of cells that characterises cancer can be triggered by a multitude of environmental factors interacting in complex ways.

What is more, we still have much to learn about the genetic basis of cancer. True, biologists have made enormous strides in determining the exact mutations involved. We know, for example, that fusion genes – those made up of two genes originally on separate chromosomes – are frequently present in some blood and skin cancers. We also know that a gene called TP53 is crucial for suppressing tumour development, and that it is the most frequently mutated gene in human cancers. Yet its range of functions remains notoriously enigmatic. Indeed, we still don't know the exact number of genes in the human genome, let alone the relationships between them or what other changes are needed for cancer to arise.

Another equally complicated area of emerging interest is the microbiome: the microbes that live on and inside the body. Each of us has hundreds of species of bacteria coexisting in our gut, and a deficiency of some or the presence of others may predispose people to cancer. *Helicobacter pylori,* for example, is an accepted causal factor in gastric cancer. Diet, hygiene and the environment all interact to influence our microbiome. As yet, we know very little about the interplay between these factors, and between the genome and the microbiome, or exactly how these bacteria promote or reduce cancer risk.

All this makes working out what causes cancer a daunting task. However, there is a way of thinking about the problem that might help. Cancer has been a fact of life, and death, throughout human evolution. As a result, we aren't totally at its mercy, because our immune system has evolved mechanisms to block the disease. One is the aforementioned TP53 which, among other things, encodes a protein that stops cancer cells proliferating. Another, known as cell cycle arrest, prevents aberrant cells from completing their normal life cycle. Paul Ewald and Holly Swain Ewald at the University of Louisville, Kentucky, refer to such mechanisms as "barriers". If in doubt about whether something is linked with cancer, they argue, we should consider whether it has the potential to weaken these barriers.

Such thinking could help explain why cancer is so common in the modern world. One reason is that people are living longer, increasing the chances that ›

DNA copying errors will lead to cancer. But another may be that we aren't behaving as we evolved to behave. An illustration of this so-called evolutionary mismatch is a shift away from breastfeeding, depriving infants of complex sugars that help nourish the gut bacteria that fine-tune their immune system. More generally, as living standards rise, children are less likely to be exposed to pathogens that prime their immune systems to fight disease later in life. Research by Mel Greaves at the Institute for Cancer Research in London suggests that a common childhood cancer, acute lymphoblastic leukaemia, may arise in this way.

By adopting modern lifestyles, then, we could inadvertently be breaking down the barriers that block cancer. If so, taking an evolutionary perspective could help researchers home in on risk factors – and guide the rest of us in judging which behaviours and substances to try to avoid. But the problem remains complex. Paul Ewald cautions that we need to look at the interplay among factors rather than simple causal chains. And Greaves notes that Western lifestyles have altered so much and so fast – a process that is ongoing – that pinpointing the changes involved in cancer won't be simple.

The good news is that we may already have the information we need. Every year, large, costly studies are launched to try to determine whether a certain substance or behaviour is carcinogenic. It is hard to sift through the mountain of data without some idea of what to look for. But evolutionary thinking can help us shine our searchlight in the right direction.

It may never be possible to identify all the interconnected factors behind a particular individual's cancer, but we can still make informed judgements about risk. Faced with the next media scare story, ask yourself whether the claim is supported by data, whether vested interests are involved and, most importantly, whether it makes sense in light of how humans evolved to live. ▮

TREATING CANCER

Cancer's ability to evolve and resist our best treatments is part of what makes it such a formidable foe. The same forces that shape the tree of life also drive tumours to spawn and spread, generating a vast genetic diversity of cancer cells within a single person. Now, thanks to recent leaps in genetic sequencing, the hope is that we can trace a cancer's evolutionary journey and create powerful treatments using this information. We might even be able to stop tumours developing in the first place.

WE HAVE known since the 1970s that tumours arise when a mutation occurs in one of the genes within a cell that control its reproduction. Our cells are continually replicating themselves – even in healthy tissues – by growing and splitting in two, to replenish those that have worn out.

This process is controlled by hundreds of genes so that cells divide at the right place and time. If a cell has a mutation in one of these genes – perhaps through exposure to cigarette smoke or ultraviolet rays or just bad luck – it may start multiplying faster, its progeny outcompeting healthy cells.

Even if the immune system attacks these cancer cells, their ability to evolve may thwart our body's attempt to destroy them. There are parallels between the way predators shape the evolution of prey populations and how immune system cells kill the most vulnerable tumour cells. It is basic survival of the fittest.

This Darwinian thinking hasn't yet influenced the mostly crude and brutal way we treat cancer, which is sometimes described as slash, burn and poison, referring to surgery, radiotherapy and chemotherapy. These approaches can work if the cancer is caught early enough, which generally means before it has spread. But chemotherapy and radiotherapy work by killing all quickly dividing cells, which means they also damage the skin, gut and immune system, causing side effects such as hair loss, sickness and vulnerability to infections.

More recently, targeted therapies have been touted as the next big thing. These work by blocking molecules on cancer cells that are specific to them, so tend to have fewer side effects on healthy tissue. This requires testing someone's cancer to identify the mutations involved, so is painted as the ultimate in personalised medicine.

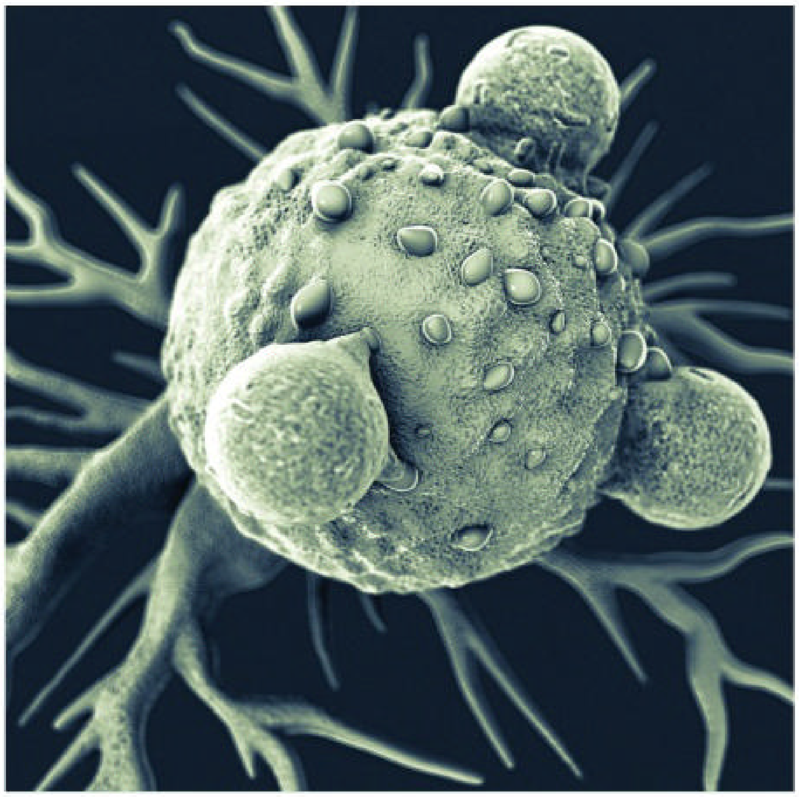
We often see media coverage when one of these new treatments reaches the clinic, but the reality is they usually extend people's lives by only a few months. Possibly, this is because their developers failed to consider cancer evolution. A targeted treatment kills all cancer cells that carry a certain molecule – but any that don't have that molecule survive. It therefore "selects for" growth of cells that are resistant to it, so within a few months, tumour cells without that molecule are more numerous, and the treatment no longer works. The cancer has developed drug resistance.

Doctors have long been aware that targeted therapies don't usually extend people's lives for long, but it is only recently that we have been able to genetically chart how resistance evolves. In a 2012 study, researchers led by Charles Swanton at the Francis Crick Institute in London, sequenced multiple samples from four people's kidney cancers, and found the cells diverged over time – the way different animal species branched off from each other over millions of years.

Within each person, two-thirds of the mutations weren't shared across all their tumour cells. This showed that it could be misleading to take one small sample from a cancer to predict which targeted therapy to use. "Depending on where you put your biopsy needle, you're going to get different results," Swanton says.

The 2012 kidney cancer paper was seen as bad news for targeted therapies, but it also showed that within each person, about a third of the mutations were present in all the tumour samples they took. These mutations must have arisen when the tumour was small, before its cells had diverged much, and are sometimes called "trunk mutations", meaning they are in the stem of the evolutionary tree, not its branches. Any therapies targeting trunk mutations should in theory kill all cancer cells and so be less likely to trigger resistance.

Swanton thinks that the best way of doing this is by weaponising the patient's immune system. People ›



LUISMMOLINA/ISTOCK PHOTOS

with cancer usually have some immune cells active against their tumour – but most target branch mutations. If someone's immune cells could be directed at their trunk mutations, this could be enough to get rid of all the malignant cells from their body.

Swanton has co-founded a firm called Achilles Therapeutics, which is due to start two small trials of this strategy this year in lung and skin cancer. When people have their tumour cut out, the firm will sequence many of its cells to identify the trunk mutations. Researchers will also extract immune cells from within the tumour and select those that target these mutations. The firm will then multiply the immune cells in the lab, so that many can be injected back into the patient.

Achilles is by no means the first to try to exploit people's immune response against their cancer. The idea has a long history and has been recently turned into a treatment called CAR-T therapy for leukaemia and lymphoma, cancers that occur when blood cells turn malignant. Using this approach against solid tumours has proved more difficult, though. Several groups have tried and failed at this – although so far none has tried genetically identifying trunk mutations.

Whether or not this approach works, a focus on evolution may lead to other treatment avenues, such as tweaking the way we use existing anti-cancer drugs. For instance, just as farmers learned that intermittent treatment with pesticides could protect their crops without causing pesticide resistance, a similar approach could pay dividends in cancer.

Researchers at the Moffitt Cancer Center in Tampa, Florida, recently found encouraging signs from an initial small test of this strategy in prostate cancer. They have now started or are planning five larger trials to put this "adaptive therapy" to a more rigorous test, by comparing it with standard treatment in prostate cancer and three other types of tumours.

In a related tactic, another team at the Moffitt Cancer Center plans to tackle a rare and aggressive form of muscle cancer by switching from one drug to a second one rather than using a single drug intermittently.

The current approach for this is to give a certain drug combination for 10 months and then wait for the cancer to recur with drug-resistant cells, which it nearly always does. At that stage, people are given a second therapy. The new idea is to give the first therapy for just three months and then immediately switch to the second. The rationale is that a small number of resistant cells must have been there all along. Hitting hard and fast with the second therapy could have more chance of killing all the cells.

Better than improving treatments for cancer would be stopping it arising in the first place. This goal is being explored for people who are at higher risk of certain tumours, again using evolutionary principles. One such group is people with Barrett's oesophagus, a condition in which the tube going from the mouth to the stomach becomes inflamed by leaking stomach acid, making them prone to cancer of the oesophagus. Those affected have a check-up every few years with a camera put down the throat and

> “Better than treating cancer is to stop it arising in the first place”

regular tissue samples taken to try to spot tumours early. But the best time to intervene is unclear. Doctors don’t want to cut out any of the oesophagus unnecessarily and some people end up getting cancer despite the screening. Perhaps we can be more accurate by considering evolution

Evolutionary theory says that, all else being equal, animal or plant species that are more genetically variable are more likely to branch into multiple new species under some new selective pressure, like a change in climate. In the same way, a genetically diverse group of cells in the oesophagus may be more likely to harbour one that can turn cancerous; the new selective pressure in this case could be a change in lifestyle, like starting smoking.

Trevor Graham at the Barts Cancer Institute in London and his colleagues put this idea to the test by sequencing the DNA of cells taken from routine biopsies of 320 people with Barrett’s oesophagus. Twenty ended up developing cancer and those who initially had more genetically diverse cells in their oesophagus were more likely to eventually get a tumour.

Offering this sequencing to everyone with the condition might enable us to decide whether people are at high risk, and should have check-ups every few months, or low risk, meaning they could be screened more infrequently.

Graham’s team has done the same study in people with an inflammatory bowel condition called ulcerative colitis, which puts them at higher risk of bowel cancer and is also monitored with regular biopsies, with similar results.

Such an approach might be applied to other types of cancer too. For instance, in the case of breast and prostate cancer, we often take biopsies from small lumps found through screening tests and don’t know if they are aggressive cancers that must be cut out straight away or slow-growers suitable for watchful waiting, sometimes characterised as “tigers” and “pussycats”.

For decades, scientists have been trying to develop a test for biopsies to tell us which kind of cancer someone has. Efforts have focused on which mutations are present but that hasn’t yet led to a useful test. Measuring the cells’ “evolvability”, based on their genetic diversity, mutation rate or other factors, might prove more effective.

This is one of many evolution-based research programmes planned by the Institute of Cancer Research. Other avenues will include developing medicines that slow down evolution, by reducing the mutation rate, and a technique known as “evolutionary steering”. This is still a theoretical concept, one that designs drugs in such a way that cells can only develop resistance to them by mutating in ways that make them susceptible to other treatments.

In the US, the National Cancer Institute began a major new programme focusing on evolution in 2018, setting up the Arizona Cancer Evolution Center. Initiatives such as these will take many years to bear fruit, but for Greaves, could provide a logical way to tackle this most fearsome of diseases. ∎

CHAPTER 6

FUTURE MEDICINE

We have made enormous progress in our understanding of disease, and in developing strategies to prevent and treat it. In the coming decades, new tools should enable us to edit our genomes and turn back the clock on our aging cells. If that fails, we may even be able to put our deteriorating bodies on ice, for some future generation to patch up.

What will these new technologies mean for human health? We kick off our discussion with an interview with George Church, a prime mover in the field of gene editing.

THE GENE EDITOR WHO WOULD REVERSE AGEING

George Church made his name as a pioneer of gene sequencing in the 90s. Since then, he has powered advances in gene editing, including being among the first to apply CRISPR technology to human cells.

A professor of genetics at Harvard Medical School and a prolific entrepreneur, Church's latest ventures include trying to persuade many more people to get their genomes sequenced and exploring ways of reversing ageing in dogs. Here, he provides a glimpse of what future medicine could look like.

How exactly does the gene-editing technology CRISPR work?

Gene editing involves snipping out a targeted DNA sequence and replacing it with another. It used to be time-consuming and imprecise, but now you can edit any living genome, using your computer to target a stretch of DNA. Guides made of bespoke RNA lead the CRISPR molecular machinery to the target, where an enzyme makes a cut. This either destroys the function of the DNA in that location or allows you to change its functioning by manipulating how the cells repair the cut, for example by inserting a genetic sequence of your choice.

What will we be able to do with CRISPR?

CRISPR could enable gene therapies that would allow physicians to fix genetic diseases, including some types of blindness, the blood disorder beta thalassemia and the neurodegenerative disorder Tay-Sachs disease. It could also mean new approaches to treating cancers and viral infections, including HIV.

Other techniques could allow helpful DNA to spread through wild animal populations, which may allow us to eliminate infectious diseases like malaria.

Some people are against any tinkering with the gene pool, fearing the advent of designer babies.

We humans already tinker with the gene pool with inherited diseases such as Tay-Sachs: genetic counselling before or after conception can help parents to decide on the health of their future children.

We tinker with the gene pool every time we fly at high altitude, which increases random mutations in developing sperm and egg cells. These things are allowed. If you don't like the concept of tinkering with the gene pool, then ban it across the board. Don't be exceptional about CRISPR.

DANIEL STOLLE

Then there's the issue of what we value. Do we value long life, intelligence, athleticism, beauty? We are already making our children more educated than their ancestors, and typically we do that without the permission of the children. People pay for products that improve beauty and athleticism. If you don't think those are good values, then ban tinkering with them. But be fair. Don't ban a particular form of it – unless it's unsafe.

For me, the safety issues are the ethical issues, and the safety issues are not fundamentally different from those of any new therapeutic. Gene-editing techniques are being extensively tested in animals, in primates as well as rodents, and will eventually move into people.

You are also working on gene editing in sperm. Why is this important?

If you have a couple that are both unaffected carriers of a genetic condition, they have a high chance of their children being affected very seriously. As an alternative to standard practice right now, abortion and IVF, you could edit the sperm to remove the faulty gene. Procreation would be indistinguishable from the usual, except you engineered some of the cells in the testes.

I have been one of the people making sure that this is in the conversation, because the gene-editing conversation tends to go to embryos rather than to sperm. And I think there is a huge difference, certainly in how acceptable they are to certain groups. For example, in 2004 a Vatican commission imagined a scenario in which editing sperm would be acceptable: it could avoid the unnaturalness of in vitro fertilisation and abortion.

But any gene editing with results that would be passed on to the next generation faces regulatory obstacles, right?

The US Congress voted for legislation that prevents the Food and Drug Administration (FDA) from evaluating the safety and efficacy of germline gene editing. They didn't explicitly ban sperm editing, but it's implicitly banned. I don't think they thought that through. The people who promoted that aspect of the bill were probably anti-abortion, but ironically that bill is delaying the arrival of technology that would reduce the number of abortions on medical grounds.

If humanity doesn't take the opportunity to advance genetic engineering in people, are we doing ourselves a disservice?

Absolutely. This question should come up more frequently. With seven billion people and growing, sitting still is not really a great option. For example, we could wipe out malaria using a gene drive – a technique that would allow a malaria-resistance gene to spread through a population of mosquitoes extremely rapidly.

That could be risky.

Some of us may say that gene drives are too risky in general because of unknown unknowns – like perhaps causing the extinction of a mosquito species. But if you did, it's unlikely that that is going to kill any other animal. And every year that we hesitate, 600,000 people die of malaria unnecessarily and another couple of million get sick and miss days at work. That's a pretty big price to pay.

You're also interested in what's called genetic augmentation. Isn't using gene therapy in that way, whether for physical or mental enhancement, controversial too?

It's less controversial because it would be in consenting adults. If a majority agrees that adults can be augmented – using a new drug, device, or gene therapy – then as long as it passes the usual safety and efficacy rules of the US Food and Drug Administration (FDA), in my view it's not controversial enough to prevent rapid adoption.

"I want the world to get used to the idea that gene therapies can be inexpensive"

You've famously come up with a list of 10 particularly protective but rare gene variants that we might all benefit from.

Yes. For example, PCSK9 protects you from cardiovascular disease, and it's "superhuman" in the sense that people who have it are well beyond the average human in terms of low cardiovascular risk. Three others on the list – MSTN, LRP, APOE – will probably lead to therapies to prevent muscle degeneration, osteoporosis and dementia.

Why do you think people are so resistant to getting their genome sequenced?

One reason is there's poor communication of its value by the press, and even by my colleagues. As a result, most people imagine that they are not at risk of having a child with a genetic disease if no one in their family has ever had one. That's far from the facts. Most infants that are born severely affected are the first in their family history, as far as the parents know.

Getting your genome sequenced could help prevent a proportion of tragic birth defects, which also cost upwards of $1 million each. You can save the healthcare system trillions of dollars.

So, you think everyone should get their genome sequenced?

I don't think everyone should do any particular thing other than breathe and eat, but probably yes, it's good public health. Ninety-five per cent of people will find there was no point in sequencing their genome, but they don't know that in advance. Imagine you are coming to the end of your life and sitting in the hospital and you say to yourself, why did I bother getting seat belts and airbags? That would be a very weird way to think about seat belts, but it's not a weird way to think about genetics, apparently.

Do you have another commercial venture brewing?

That's a complicated one: we have 13 start-ups coming out of my lab alone. One of them, Rejuvenate Bio, is working on ageing reversal – in dogs, initially. One of the reasons is we can make the cost much lower. The FDA approval for veterinary products is a lot faster and cheaper, and I want the world to get used to the idea that gene therapies can be inexpensive. Dogs are a really good product target, but they are also a good segue to humans because they are similar in size, they live in our environment, they eat our food, we are responsive to their emotional state. In many ways, they are like children.

We want to do this in dogs that are at least 11 years old. We have tested ageing reversal in mice that are at least 2 years old – mice almost dead with ageing.

What do you really mean by ageing reversal?

Well, there are acute diseases where the recovery is faster in young animals: for example, heart problems in which there is essentially no recovery when you're old, but it is very fast when you're young. So, we are looking at things like how gene therapy can aid recovery from cardiac damage, kidney problems, obesity, diabetes – a lot of things that really only kill old people, only kill dogs that are over 10 years old.

Ageing reversal is a much better target than longevity. It's very difficult to get the FDA to approve a drug that will make you live 20, 30 years longer. The FDA requires you to prove exactly what you want to put on the label, so if you want to put 30 years of added longevity, you have to do a 30-year study. We're saying we can achieve ageing reversal in maybe a couple of months, so then our study can be that short.

Do the animals you are treating look the same afterwards?

The mice look the same. Perhaps a little friskier. ▮

WHEN ORGANS REPAIR THEMSELVES

STEM cells are the blank slate from which the body can build any type of cell it needs. Most versatile are embryonic stem cells (ESCs), found in three to five-day embryos, which can differentiate into any tissue type. Adult stem cells, on the other hand, are found in adult bone marrow, fat, and possibly other tissues such as the heart and brain, albeit in small numbers. Compared with ESCs, these have a more limited ability to give rise to various cells of the body. For instance, bone marrow stem cells can give rise to various types of blood cell, but they cannot grow a new brain.

For a long time, biologists assumed that other types of adult cells were largely stuck with their fates. Once ESCs had differentiated into skin cells, heart muscle cells, neurons or whatever, there seemed to be no turning back.

But in 2006, Shinya Yamanaka, then at Kyoto University in Japan, disproved this in spectacular fashion. He transformed adult mouse cells back into a stem-cell-like state by inserting a cocktail of proteins called transcription factors. These work by changing which of the cells' genes are expressed, switching the cells to a "pluripotent" state in which they are able to differentiate into any tissue in the body. A year later, Yamanaka repeated the trick with human cells, a breakthrough that earned him a share of the Nobel prize for medicine in 2012.

Yamanaka's induced pluripotent stem (iPS) cells promised a new era of medicine. They provided a means to skip over the ethical quagmire associated with acquiring stem cells from discarded embryos. They also offered an abundant source of therapeutic cells that the immune system shouldn't reject because they could be grown from the transplant patients themselves. The hope was that cells, tissues and perhaps entire organs would soon be grown in the lab from mature cells from a patient, before being transplanted back to repair injury or cure disease.

More than a decade after Yamanaka's discovery, however, iPS cells have yet to deliver. Only a handful of stem-cell therapies have been approved by the US Food and Drug Administration – for several blood disorders, including leukaemia, and skin growth after burns – and all of those make use of embryonic stem cells, not iPS cells.

The failure has been felt acutely in the world of cardiology. Heart disease is the leading cause of death worldwide and there is often precious little we can do about it. Pacemakers bring some relief and transplants work, but there are nowhere near enough donated hearts to go around. And unlike skin and liver cells, heart muscle cells can't remake themselves. Once they get damaged or die, they are gone forever.

←
Page 48 has a discussion of the use of statins to prevent heart disease

iPS cells were initially hyped as a solution, but no cell-based therapy is close to being approved for heart disease. There are several possible reasons: For one

The idea of growing replacement organs outside the body has so far largely disappointed. But over the past few years, cell biologists have been quietly exploring an alternative approach: switching their identities in situ, so that we can heal ourselves from within. If we can perfect the tricks needed to safely do this – and it is a big if – we should be able to repair tissues ravaged by all sorts of conditions, from diabetes to dementia.

thing, there are still questions about how closely iPS cells resemble real stem cells, and so how versatile and safe they are. Then there is the fact that lab-grown cells, once transplanted, struggle to integrate with surrounding tissue.

These setbacks have spurred researchers to start exploring an alternative approach that doesn't involve grafting lab-grown cells. The idea is to exploit the plasticity of cells by transforming them inside the body rather than reverting to a pluripotent state first. And you have to do this directly, because iPS cells made inside animals have a tendency to turn cancerous.

Deepak Srivastava at the Gladstone Institutes in San Francisco and his colleagues were the first to demonstrate such "direction conversion" of heart cells in 2010, when they transformed mouse heart fibroblasts, which make up some of the fabric of the organ, into beating heart muscle cells or cardiomyocytes, using just three transcription factors. Later, they went one better by getting those cells to beat in a coordinated fashion, just as in real cardiac muscle. In 2013, they pulled off the trick in human cells too.

Clearly, then, you don't need to wipe the slate clean to transform cells. The trouble is, Srivastava and his colleagues only did all this in cells grown in a Petri dish, where it is easy to deliver the reprogramming agents and control the environment in which they grow. But to avoid the complications associated with transplantation, we need to do it inside the body. This is where things get trickier.

We already have the means to deliver genetic material encoding the proteins needed for transformation, using methods developed for gene therapy. Typically, the genes are delivered by a virus that does not integrate any of its own DNA into target cells' genomes.

Several groups have now used such methods to directly convert cells inside animals. In 2008, for instance, a team led by Douglas Melton at the Harvard Stem Cell Institute transformed ordinary pancreatic cells in mice into insulin-producing beta cells, those destroyed by an autoimmune response in people with type 1 diabetes. Sure enough, the converted cells produced insulin – an encouraging proof of principle.

But making insulin-producing cells is probably one of the easier hurdles to clear for in vivo cell reprogramming. Even if you make them from liver cells, as Jonathan Slack, then at the University of Minnesota, and co-workers have done, the switching required is relatively minor because the two types of cell come from the same precursor cells in the growing embryo. What's more, these beta cells don't have to fully assimilate with the cells around them to produce insulin.

The same cannot be said for heart muscle cells, which need to coordinate their pulsing activity with the rest of the heart. Nevertheless, in 2012, Srivastava and his team managed to reprogram heart fibroblasts into muscle cells within living mice by injecting them with the genetic instructions for three transcription factors. The mice had suffered a heart attack, producing scar tissue that impaired cardiac function. But a couple of months after the treatment, their hearts had begun to recover. Some of the scar tissue had been converted into beating heart muscle cells and the organ's ability to pump blood had improved. ›

One obvious concern is that, once injected into the body, gene-tweaking proteins might run amok, drifting away from the place they are supposed to work and transforming other cells elsewhere. On the other hand, the experience of gene therapy indicates that it is very hard to get enough genes into even the target tissue, so off-target effects may not be a big risk.

Even so, gene therapy has a chequered past. The most notorious failure was the 1999 trial in which an 18-year-old called Jesse Gelsinger died after reacting to the virus used to deliver the therapeutic genes to his tissues. The tragedy left the field in limbo for years. And although researchers have since demonstrated that a new generation of viral vectors are safer, leading to a resurgence of clinical trials of gene therapy for otherwise intractable diseases, there are still legitimate fears.

It is also why people are keen to explore virus-free alternatives, most notably the use of small synthetic molecules instead of genes to do the reprogramming. Srivastava's team, for example, has converted human cardiac cells with small molecules of this kind. The long history of using such compounds as drugs should make it easier to get them through the regulatory system. Possibly, they could even be administered in creams or injections to rejuvenate skin, muscle or bones.

San Francisco-based Tenaya Therapeutics, spun out of work done at the Gladstone Institutes, is already forging ahead with gene-based reprogramming. The company is aiming to switch cells in vivo with genes delivered by viruses, to restore function in hearts that have lost cardiac muscle after a heart attack.

Meanwhile, Srivastava has been pursuing what could be an even better way to repair tissue from the inside: not by repurposing existing cells, but by stimulating the growth of new ones. Earlier this year, he and his colleagues found they could trigger the multiplication of cardiomyocytes in adult mice with yet another mixture of genes, this time ones normally involved in regulating the "cell cycle" that governs proliferation during the gestation of the fetus.

When the team injected the genes into adult mice with damaged hearts, the animals generated fresh muscle, something that would never normally happen. Srivastava says it is the first time anyone has been able to get adult cells to start dividing anew efficiently enough to make the approach viable for clinical use.

What about the brain? With the exception of two small regions, adult brains cannot make new neurons from scratch. There is a short window of time after injury when it attempts to clear away debris and reroute its connections to regain some of the lost function. Some drugs, if given within a few hours, can also stop the damage from becoming too severe. Even so, the fact that dead neurons can't be replaced can mean that the damage done leads to lifelong disability.

However stem cells, with their ability to generate various cell types, hold the potential to fix many kinds of brain damage. Brain tissue is composed of various cells, including neurons, support cells, connective tissue and blood vessels. Early attempts at cell replacement had shown it was possible to squirt cells into an injured brain without causing further damage. The question was whether stem cells could get in there and rebuild the complex structure of what had been lost.

Animal studies looked promising. Rats injected with stem cells following a stroke recovered sensation and movement to a degree rarely seen before. On closer inspection, though, there was a surprise. The reason it worked wasn't because dead and dying cells had been replaced with shiny new ones, though this did happen to some extent. Even when stem cells remained in their immature state, or didn't survive for longer than a few weeks, they still contributed to the animals' recovery.

What seems to be happening is that stem cells release growth factors and other chemicals that stimulate the brain to heal itself, potentially giving compromised circuits the ability to regroup and reorganise. Some of these chemicals may also boost the immune system, reducing inflammation and helping to stimulate blood vessel growth – all crucial if a mended bit of brain is to thrive. In fact, it could even be that this plays a more important part in brain fixing than cell replacement.

So far, though, no one knows for sure what the stem cells are doing in the brain. This has led some to argue that even if it works, we should hang back from using it on patients because it would be unethical to proceed. Others think it would be unethical not to.

Whatever the rights and wrongs of that argument, clinical trials are under way. Already, two companies – ReNeuron in Pencoed, UK, and SanBio in Mountain View, California – have reported data from phase 1 clinical trials using stem cells to improve disability following stroke. Both have reported good safety data, and intriguingly, the first glimpse of efficacy, with most patients showing a significant improvement in control over their limbs, or the loss of a tremor. And despite the cells themselves only lasting a month or so after the injections, the improvements seem to linger way past the six months after which stroke patients are usually told to expect no more change.

The implications of such treatments could be profound. Ultimately it may not be necessary to repair and replace tissues by putting existing cells to new uses. No changes of identity would be necessary. We could simply persuade our broken hearts, and perhaps even our degenerating brains, to grow again. ■

A PILL AGAINST AGEING?

If our cells become damaged, they can either undergo programmed cell death or enter a senescent phase, in which they stop dividing. One theory is that these senescent cells send out chemical signals which inform their neighbours there is a problem, enabling them to intervene. This may be helpful when you are young, but the longer these cells stay there, the more of these products they secrete, resulting in long-term inflammation and organ damage. Enter senolytics: a new class of drugs that seek out and destroy senescent cells.

FROM a biological point of view, ageing is essentially the progressive loss of the body's ability to repair itself. As our repair processes fail, damage proliferates. Organs and tissues clog up with clumps of protein and other detritus. Genetic mutations accumulate. Chromosomes start to unravel. Some cells become cancerous, others turn into zombies. Immune defences weaken. The powerhouses of our cells, mitochondria, fall into disrepair. Low-level inflammation, called inflammaging, creeps through the body.

Thank science, then, that we now know enough about those repair processes to try rebooting them with drugs. A lot of the smart money is on a class of drugs called senolytics, which seek out and destroy the worn-out cells that build up as we age. These cells have suffered some sort of irreversible damage and entered a state called senescence where they hit the emergency stop, hunker down and await destruction.

This process probably evolved to stop cells from becoming cancerous. But it eventually backfires. The cells are like zombies: beyond repair, yet undead and pumping out a range of inflammatory proteins that cause havoc. Senescent cells are now known to cause many age-related diseases, including cancer, atherosclerosis, type 2 diabetes, osteoarthritis, Parkinson's, Alzheimer's and cataracts. Tellingly, if you take senescent cells from an old mouse and transplant them into a young one, it ages prematurely and acquires the diseases of old age.

The opposite is also true. If you remove senescent cells from old mice, their condition improves. Recently, Darren Baker at the Mayo Clinic in Minnesota, and colleagues tested senolytics on a cage full of very old mice. They didn't miraculously rejuvenate, but their decrepitude eased.

One great advantage of senolytic drugs is that people could take an occasional dose, perhaps once every six or 12 months, to clear out the cellular trash. Most other anti-ageing drugs would probably have to be taken much more regularly, which raises safety concerns.

If you are wondering when these drugs might be available, the answer is soon. Maybe. The usual caveats about the vagaries of drug development apply, but from where we are now, they could be in the clinic in as little as five years.

Already, they have entered human trials. In January 2019, a team led by Mayo Clinic researchers reported results from a pilot trial targeting a lung disease called idiopathic pulmonary fibrosis. Its cause is unknown, but the disease is characterised by a build-up of senescent cells. In the trial, 14 people were given doses of two drugs – a leukaemia treatment called dasatinib and a plant pigment called quercetin – over three weeks. They tolerated the drugs well and showed some improvements in symptoms.

That is miles away from being proof they cure › anything. But also in January 2019, Unity Biotechnology, a firm seen as one of the companies most likely to succeed, announced promising results from an early clinical trial of a senolytic for osteoarthritis.

If these front-line attempts fail, there are plenty more. Two other companies, Cleara Biotech and Senolytic Therapeutics, are developing drugs. Another approach is "senomodifiers", which don't kill senescent cells, but coax them to start dividing again. The most promising senomodifiers are based on resveratrol, a natural compound found in grape skin. In experiments on yeast, resveratrol extended lifespan by up to 50 per cent. Further over the horizon are molecules that can rejuvenate white blood cells and restore their prowess at clearing senescent cells.

Another hot area is a new take on an old anti-ageing strategy: caloric restriction. Play buzzword bingo at a conference on ageing, and "senolytics" would be top of your list. But a close second would be "mTOR". This is a protein complex inside cells that plays a critical role in ageing, and which gerontologists have long believed could be targeted to slow the process down. mTOR is an acronym for "mechanistic target of rapamycin", which tells you more about how biochemical knowledge advances than what mTOR actually does. The keyword is rapamycin, a drug developed as an immunosuppressant for transplant patients that later turned out to extend lifespan in worms, flies and mice. Biochemists discovered it was interacting with a protein complex in the cell. They named this mTOR and set about working out what it did.

What they discovered made biological sense. One of the most reliable ways to make an animal live longer is to starve it. Caloric restriction and periodic fasting have been shown to extend both lifespan and healthspan in every animal they have been foisted on, probably because they activate some of the protective pathways that are progressively blunted by ageing.

The mTOR complex turned out to be a crucial hub in this system. Its key function is nutrient sensing. If you eat, it is activated and tells the cell to grow and divide. If you don't eat, it switches off, upregulating protective pathways.

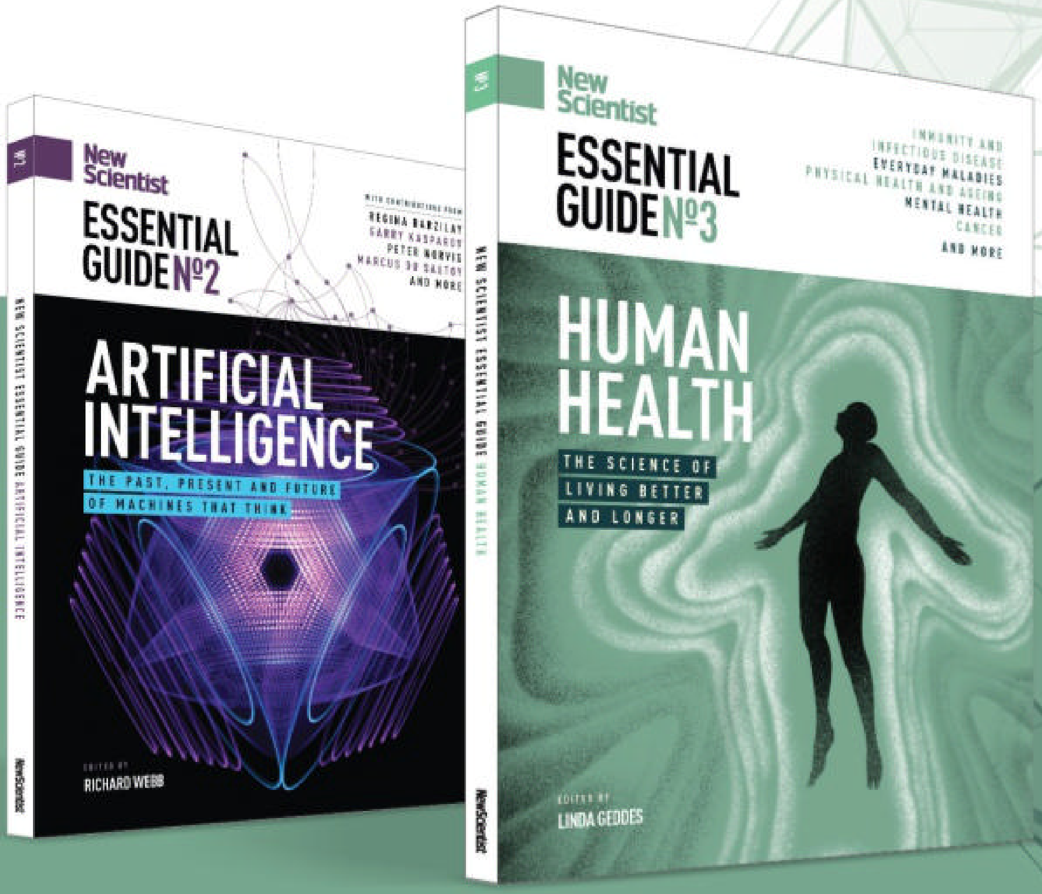
These pathways include autophagy, the process by which cells scavenge dysfunctional organelles and molecules for energy. This reduces the accumulation of the gubbins that would otherwise build up in tissues, and hence slows or even reverses the ageing process. Intriguingly, mTOR seems to become progressively stuck in the "on" position as animals age.

Actual starvation isn't necessary: rapamycin is just one of many drugs known to inhibit mTOR in mice even when they are first given it only late in life. And just as with senolytics, the science is now being turned into therapies for humans.

In 2018, resTORbio published the results of a clinical trial to see whether mTOR inhibitors can reverse immune system ageing. In it, 264 people over 65 were given two drugs – not rapamycin itself, but newer compounds that work in a similar way – followed by a flu shot. Older people often fail to respond to the injection and influenza is a major cause of hospitalisation and death among this group. But those given mTOR inhibitors responded much more powerfully to the shot and caught fewer respiratory infections. A bigger clinical trial confirmed the effect, but the drug failed to clear the final phase of regulatory approval early in 2020 – on a technicality, the company says.

If any of the drugs should succeed, it would be a medical landmark: the first of a new generation of medicines specifically designed to target ageing. And there is no shortage of promising avenues to hit mTOR or targets up or downstream of it. The pathway has long been implicated in cancer, heart disease and neurodegeneration, so many existing drugs for all sorts of diseases target it. Plenty of these drugs have now been tested for their anti-ageing properties in a programme run by the US National Institute on Aging. It puts promising compounds through their paces in mouse experiments at three facilities. It has validated six compounds, as well as eliminating some promising ones, including the diabetes drug metformin. Most of the winners inhibit the mTOR pathway, but some work in mysterious ways, suggesting that there are still things we don't know about the basic biology of ageing and hence new avenues to explore.

It is still early days. But it is possible that within a decade, those approaching sixty won't be facing the usual descent into decrepitude, but a long and productive third age. For all our futures, let's hope so. ▮



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FREEZING OUT DEATH

Advances in medicine have significantly extended human lifespan and are now making inroads on "healthspan" – the number of disease-free years towards the end of life. Even so, few adults can be certain of seeing in the next century. In Texas though, a disaster-proof complex has been built that will house 50,000 frozen people. Their hope is to be reanimated in an even more distant future.

CRYONICS, the cooling of humans in the hope that one day technology will be able to bring them back to life, has a reputation as a vanity project for those who have more money than sense. Yet, in the last few years, the discipline has made remarkable inroads. As well as bodies, Timeship, the new Mecca of cryogenics in Comfort, Texas, will store cells, tissues and organs, in a bid to drive forward the capabilities of cryogenics. Its cutting-edge facilities should break through the limitations of current cryopreservation, making it more likely that tissues – and whole bodies – can be successfully defrosted in the future.

Timeship is the brainchild of Bill Faloon and Saul Kent, two entrepreneurs and prominent proponents of life extension research. Their vision was to create a building that would house research laboratories, DNA from near-extinct species, the world's largest human organ biobank, and 50,000 frozen bodies. Kent called it "a plan to conquer ageing and death".

At body temperature, cells need a constant supply of oxygen. Without it, they start to die and tissues decay. At low temperatures, cells need less oxygen because the chemical activity of metabolism slows down. At very low temperatures, metabolism stops altogether. The problem faced when trying to preserve human tissue by freezing it is that water in the tissue forms ice and causes damage. The trick is to replace the water with cryoprotectants, essentially antifreeze, which prevent ice from forming. This works well for uncomplicated structures like sperm and eggs. But when you try to scale it up to larger organs, damage still occurs.

But in 2000, Greg Fahy, a cryobiologist at 21st Century Medicine in Fontana, California, made a breakthrough with a technique called vitrification. It involves adding cryoprotectants, then rapidly cooling an organ to prevent any freezing; instead the tissue turns into a glass-like state. Fahy later showed that you could vitrify a whole rabbit kidney that worked after thawing and transplantation.

Timeship's architectural plans make it look like something between a fortress and a spaceship. The central building is a low-lying square with a single entrance. This sits inside a circular wall surrounded by concentric concrete rings. Inside are collections of thermos-like dewars to store cryopreserved DNA, organs and bodies.

It may seem an extravagant endeavour, but in fact the strongest argument for such a facility, and the technological developments it promises, might have nothing to do with the desire to be frozen for the future. We already have small biobanks for storing bones from human donors, as well as tendons, ligaments and stem cells. But with advances in regenerative medicine, there is a growing need for large-scale facilities in which we can store more cryogenically frozen biological material.

Stem cells, for instance, are increasingly cryopreserved after being extracted and grown outside the body for use in regenerative therapies. Then there's the problem of organ shortage. In the US, almost 31,000 transplants were carried out in 2015, but at least six times as many people are on the waiting list – each day 12 people die before they can get a kidney. To make matters worse, many organs go to waste because their shelf life is too short to find a well-matched patient. Nearly 500 kidneys went unused in the US last year because the recipient couldn't get the organ in time.

So, there's an urgent need to be able to store whole organs for longer. We can already reversibly cryopreserve small bundles of cells – many thousands of babies have been born from vitrified human embryos. Doing the same with large organs, like kidneys or hearts, is harder, but not impossible. Over the past decade, several babies have been born from ovarian tissue that was removed before chemotherapy, cryopreserved and later replaced. Similarly, rabbit kidneys and rat limbs have been cryopreserved, thawed and placed in a new body. Having improved both the vitrification technique and the cryoprotectant solution, researchers are moving to trials in pigs. Human trials could follow within five years.

That might help prevent wastage, but we would still have a shortage of organs for transplant. Another solution is to grow them from scratch using our own stem cells and keep them until we need them. So far, tiny 3D heart-like organs have been made from stem cells alone, as well as mini kidneys and livers, all with the ultimate aim of bioengineering replacement organs for transplantation.

Once organs can be produced like this, we will need a way of storing either the raw material or the organs themselves. Many scientists are optimistic about the prospects of bringing individual cryopreserved organs back to life. However, they are less convinced by the idea of freezing whole bodies.

Currently, most facilities offering this service to the recently deceased first replace all the blood in the body with medical-grade antifreeze. This is to prevent any ice crystals from forming as they gradually cool the body, first with ice, then liquid nitrogen, eventually taking it all the way down to -196 °C.

Alcor Life Extension Foundation in Scottsville, Arizona is the world's biggest cryonics facility. Recently, Alcor scientists placed acoustical devices on the brains of "neuros" – people who have opted to have their head frozen after death – as they were lowered into liquid nitrogen, listening as the heads cooled to -196 °C. The colder they got, the more frequently the team heard acoustical anomalies, which they attribute to tissues micro-fracturing. It's difficult to say what effects this might have, but it doesn't happen until around -140 °C.

But to store a person at above this temperature, you have to keep them warmer than nitrogen's boiling point, which is very hard to do – certainly much harder than placing a body in a giant thermos full of liquid nitrogen, letting it boil and occasionally topping it up.

At Timeship, Stephen Valentine thinks he's cracked the problem. After years of experimentation, he has designed a system called a Temperature Control Vessel (TCV), a dewar that houses cryogenically preserved bodies, heads or tissues. Inside the dewar are moving rods that can be dipped into a pool of liquid nitrogen whenever a sensor notes that the temperature has risen from -140 °C, a relatively autonomous way of maintaining the contents at an ideal temperature.

Each TCV can carry hundreds of samples of tissue and organs, or four bodies and five heads. They are designed to be stacked together in a tessellating pattern that forms the neighbourhoods within the main building.

This should reduce some of the damage to brain tissue that the Alcor team heard. But even with that technology, is there any hope of reanimating a brain?

There is some evidence to suggest that certain properties of the mind – memories, for instance – can survive cryopreservation. In 2015, researchers trained worms to recognise a smell, then froze them. On ›

STSMHN/ISTOCK PHOTO

thawing, the worms retained the smell memories. And this year, Fahy's team cryopreserved a rabbit brain in a near-perfect state. Although the group used a chemical fixative that is not yet used in human preservation, the thawed rabbit brain appeared "uniformly excellent" when examined using electron microscopy.

Not everyone is convinced. Even if the delicate structures of the human brain can be preserved, the cryoprotectants themselves are toxic and so may cause further damage.

There are precedents for the idea that the human brain can be revived after being cooled, however. In 1986, two-year-old Michelle Funk fell into an icy creek where she was submerged for just over an hour. Despite showing no signs of life, doctors spent 2 hours warming her blood through a heart-lung machine. Eventually, she recovered fully. Her doctors figured that the sudden cooling of her brain must have slowed the organ's need for oxygen, staving off brain damage.

Funk's recovery was so remarkable it spurred researchers to repeat the scenario experimentally in pigs and dogs, cryopreserving them for hours before bringing them back to life. The same procedure is now being tested in humans in a trial by surgeons at UPMC Presbyterian Hospital in Pittsburgh, Pennsylvania. They are placing patients in suspended animation for a few hours, to buy time to fix injuries that would otherwise be lethal, such as gunshot wounds. The technique involves replacing the person's blood with a cold saline solution and cooling the body. They will then try to fix the injuries and bring the patient back to life by slowly warming the body with blood.

That's not so different from what goes on at Alcor. "What we're doing is trying to stretch the time in which the person is suspended," says Max More, the president and CEO of Alcor. "It's just an extension of emergency medicine. Who is to say that in 100 years we won't have the medical tools – some kind of nanotechnology perhaps – that can fix cells at an individual level and repair what's necessary to revive someone in good health."

This is the central argument in favour of cryonics – the possibility, no matter how slim, that it offers a chance of survival. It's a long shot, and an expensive one at that. Cryopreserving your body will set you back up to $220,000, payable on death – often via life insurance, with Alcor as the beneficiary.

Assuming you're happy to fork out, and you're reanimated without suffering brain damage, there's also the big question of what kind of future you'd wake up to. Could you expect to fit in with a futuristic culture, or would you be a lonely freak, so culturally isolated you were at risk of being driven mad? ▮

WHY I'M HAVING MY HEAD FROZEN

Taking out insurance to freeze your head after you die is the responsible thing to do, says the futurist author D. J. MacLennan

Ever since I learned that people eventually died, I have had this fear of death churning away in the background. As a child I was always thinking "isn't there something we can do about this?"

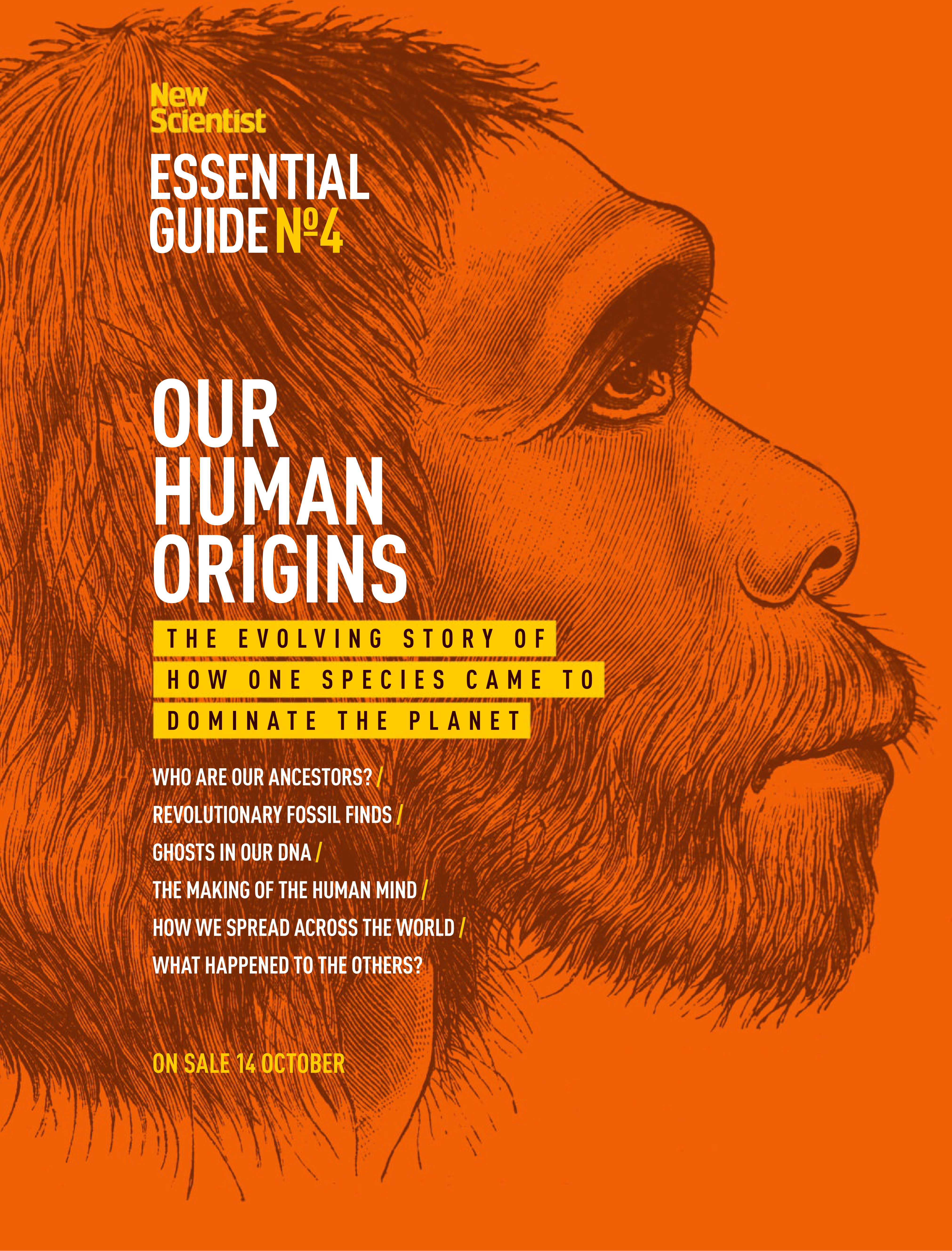
I considered cryopreservation for many years and then signed up as a neuro – which means I'll only have my head preserved – in 2007. It made perfect sense to me that the mind arises as an emergent property of the brain and that it might be possible to preserve that.

I don't know whether it will be possible to bring someone back because it's hard to know what kind of repair work you would have to do to correct any deterioration. Is it a case of engineering viruses or blood cells that are available now, or using nanomachines to move atoms around in order to fix clinically dead brains? Or will it need technology that isn't even close to existing right now? Our brains might even just be scanned into a computer at a molecular level and made up of algorithms. We just can't predict what will happen, but I see it primarily as an engineering problem.

I discussed it with my wife for several years, but didn't tell anyone else until I'd signed up. My parents and siblings realise I'm not a crazy person, so they're generally supportive. But it is really hard for a lot of people to understand; you're asking them to completely overturn their views of the finality of death. If you believe, for religious or philosophical reasons, that the self is something other than an emergent property of the architecture of the brain, then cryonics makes no sense at all.

I don't agree with people who say it's unethical. Where's the wisdom in losing the accrued knowledge of someone who's lived for decades? I think death is a terrible, terrible thing. Giving yourself the option, however minute, of keeping hold of all that knowledge and experience is surely the responsible thing to do."

D.J. Maclennan is the author of *Frozen to Life: A personal mortality experiment*



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